proven idiopathic origin is good Prognosis of such cases associated with other conditions like brain tumors Parkinson's disease and xanthomatosis depends largely on the underlying pathological condition

Contrary to the belief of some individuals patients have lived for 10 to 45 years or even longer without showing any scars due to this disease Persons who have inherited the disease have an especially favorable prognosis as one can see from the longevity of the cases in the Weil[1 11] pedigree Three of their patients lived to the ripe ages of 83, 87 and 9 years The study of Forssman[1] corroborates Weil's results Apparently patients with this disease may look forward to a long life expectancy unless some intercurrent condition appears However a number of these intercurrent diseases such as infections which appeared frequently in the old days are unlikely now because of modern therapy and hygiene which prevent debility and treat complicating conditions

The excessive consumption of water over a period of years does not have a detrimental effect on the cardiovascular system Arteriosclerosis is relatively uncommon in diabetes insipidus

A person with this disease should be expected to live a normal life Psychologically people with diabetes insipidus can live happily and usefully They should not feel inferior or hindered because of their disorder Children with diabetes insipidus should be considered a normal part of the household and their parents should plan their future in the same way they would for healthy boys and girls

Patients with diabetes insipidus may marry and have a happy marital life Normal pregnancy and normal delivery are to be expected Furthermore the disease may improve during pregnancy Surgery when necessary can be performed and any type of anesthesia employed without any greater risk than normal

A person with diabetes insipidus is a normal individual mentally and emotionally whose major defect lies in the supraoptic hypophyseal system which regulates the secretion of the posterior lobe of the pituitary gland Medical science may now control this dysfunction These people whether young or old should take a normal place in society

Treatment

The ideal treatment of diabetes insipidus naturally is the eradication of the cause if possible Unfortunately the successful treatment of the cause of this disease is quite rare However it is now possible to

control the polyuria and polydipsia by the administration of posterior pituitary extracts Of importance for the patients' comfort posterior pituitary therapy relieves these symptoms regardless of the etiology of the diabetes insipidus

Posterior Pituitary Therapy

In 1913 von den Velden and Farini[3] independently found that extracts of the posterior lobe of the pituitary gland relieved the polyuria and the polydipsia of human patients with diabetes insipidus This observation led to the treatment of diabetes insipidus with posterior pituitary solution So far none of the active principles of the posterior lobe of the pituitary gland has been isolated in chemically pure form Abel and associates[109] have isolated a tartrate of high purity possessing pressor oxytocic and antidiuretic properties Kamm and associates[110], as well as Stehle[111] and other investigators have separated from pituitary extract two fractions namely pitressin and pitocin Various preparations of the posterior lobe of the pituitary gland are available for clinical use

Forms of Extracts of Posterior Pituitary — Nomenclature and Potency —According to the U S Pharmacopeia XIII, 1947[41] the three synonymous designations for the soluble extract of the posterior lobe of the pituitary gland are *posterior pituitary solution*, *pituitary solution* and *posterior pituitary injection*

Posterior pituitary solution, or its equivalent, is a solution in water for the injection of the water soluble principles of the posterior lobe of the pituitary body of healthy domesticated animals used for food by man The potency of posterior pituitary solution is such that 0 1 c c of the solution possesses an activity equivalent to 1 U S P posterior unit The potency of 0 5 mgm of U S P posterior pituitary (standard) represents 1 U S P unit

Posterior pituitary is the official title of the powdered extract of the posterior lobe of the pituitary gland It is the clean dry and powdered posterior lobe obtained from the pituitary body of domesticated animals used for food by man The potency of posterior pituitary is such that 1 milligram possesses an activity equivalent to not less than 1 U S P posterior pituitary unit

Pitressin tannate in oil, a compound solution of posterior pituitary with slow absorption and a greatly prolonged antidiuretic effect, is a

water soluble chemical combination of the pressor fraction of · posterior lobe of the pituitary gland with tannic acid The pressor fr tion is precipitated with tannic acid and the precipitate is removed filtration washed and dried under aseptic conditions Five pressor ui of pitressin tannate are suspended in 1 c c of peanut oil

Commercial preparations —The word *Pituitrin* identifies the mai factured extract of the posterior pituitary gland This commerc preparation is obtained in two strengths (1) obstetrical pituitrin co taining 10 units per c c and (2) surgical pituitrin containing o ui per c c Surgical pituitrin is twice as strong as obstetrical pituitrin a has twice the oxytocic potency of pitocin

Pitressin which contains 20 pressor units in each c c is of · same strength as surgical pituitrin and designates the pressor blo pressure raising and antidiuretic principles of the posterior lobe the pituitary gland in a solution substantially free from the oxyto principle One pressor unit is the pressor activity exhibited by milligram standard U S P posterior pituitary powder Pitressin inste of pituitrin should be used in diabetes insipidus with pregnancy avoid the oxytocic effect

One gram of posterior pituitary powder U S P is the equivalent six grams of fresh posterior lobe pituitary substance It contains all i principles of pituitrin

Since the expense of these items is an important factor to ma patients the comparative cost of the various preparations is listed belo

Preparation	*Amount*	*Co*
Posterior pituitary powder	4 grams	$:
Posterior pituitary powder	100 capsules 45 mgm	$
Pituitrin obstetrical strength	100 1 c c ampoules (o units)	$
Pituitrin surgical strength	100 1 c c ampoules (20 units)	$5:
Pitressin	100 1 c c ampoules (20 units)	$4
Pitressin tannate in oil	100 1 c c ampoules (5 units)	$3:

Administration of Posterior Pituitary Extract – The preparations posterior pituitary may be administered by several methods The sol tion may be given subcutaneously intramuscularly and intranasal The powder may be taken intranasally Pitressin tannate in oil may administered subcutaneously or intramuscularly The dose of posteri pituitary solution is 5 to 1 0 c c when injected and is required two four times a day There is an immediate drop in the fluid intake a output after the administration of this extract and when the drug

omitted there is a rapid rise in the intake and output to the original level Fig 1 illustrates the effect of posterior pituitary solution in a patient

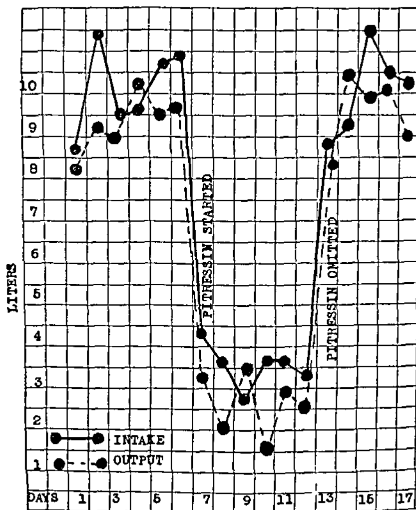


Fig 1 Effect of the injection of 1 cc of pitressin 4 times a day on the daily fluid intake and output of a patient with diabetes insipidus

with diabetes insipidus The effect of each injection lasts for about five to eight hours depending on the individual patient However most patients do not take pituitary solution as soon as the effect wears off, consequently many are not under complete control at all times as when pitressin tannate in oil is taken

Posterior pituitary solution should be used at the specific times which give the patient most comfort from the polyuria and polydipsia at his bedtime to insure a good night s sleep in the morning on arising and during the day whenever necessary In the treatment of a patient in the hospital ward it is important to specify the exact time of the therapy Otherwise if an order is written for pituitary solution three times a day it is likely that it would be administered at 10 00 A M 2 00 P M and 6 00 P M or *it would fall into the hospital s routine three times a day* orders when most drugs are given

The effectiveness of the intranasal application of posterior pituitary was demonstrated first by Blumgart [4] He showed that it checked the polyuria and polydipsia almost as effectively as the hypodermic injection the frequent administration of which often causes the patient discomfort This method is not accompanied by unpleasant gastrointestinal and circulatory reactions

The pituitary extract may be sprayed into the nose so as to be deposited mostly in the roof of the nasopharynx or the extract may be applied by the means of a cotton pledget the last being a most effective method A piece of absorbent cotton the size of the end of a finger is soaked with 5 or 1 c c of the posterior pituitary solution by filling a 1 c c syringe with the desired amount inserting the needle into the cotton and discharging the content of the syringe it also may be soaked by dipping the cotton into the posterior pituitary solution vial The cotton then is saturated by light squeezing so that no pituitary extract will be lost The pledget then is taken with a forceps and deposited in one nostril at the level of the middle turbinate where it should be kept for about three or more hours to permit a continuous absorption If the cotton pledget is too low in the nostril little absorption takes place Generally the nostrils should be alternated The nose frequently becomes irritated and sensitive and the patient has the sensation of a cold

My experience has shown that this form of treatment is effective in all cases but that it may produce less marked results than the pituitrin injection Yet when the pituitary solution is applied intranasally in more frequent doses it has approximately the same effect as the subcutaneous injection I have found that posterior pituitary solution administered sublingually and between the gums and mucous membranes of the mouth has afforded some relief but not enough for practical purposes This solution also is absorbed to a slight degree when applied intra vaginally

It has been shown[113] that the intranasal insufflation of posterior pituitary powder in doses of from 40 to 50 milligrams three times a day is as effective in maintaining a normal water balance with alleviation of all symptoms as 1 5 to 2 0 c c of double strength solution of pituitary administered subcutaneously The usual patient requires three to four such doses a day to maintain a water balance with alleviation of the polyuria and polydipsia The effect of each dose varies from four to eight hours

Insufflation outfits may be used for the introduction of posterior pituitary powder into the nose but they must be clean and dry The nozzle must be inserted about three quarters of an inch inside the nose in order to be high enough Then the breath is held and the bulb of the insufflator is squeezed with sufficient force to propel the powder on to the upper absorptive surfaces of the nose The process may then be repeated in the other nostril Excessive force should not be used in blowing the powder into the throat The nose should not be blown for some time after the administration of the powder The posterior pituitary powder also may be inhaled by taking a pinch of it from the finger tips or by inhaling it from a snuff box

Choay and Choay[114] have used poterior pituitary powder inhalation for twenty years to control the thirst and polyuria in more than 100 cases of diabetes insipidus The powder was taken into the nose in the manner of snuff Their best results were obtained with three to five doses of 0 01 gm in the course of a day and with one dose of 0 02 gm at night before the patient went to bed In the average case they found that the effect lasted three to six hours during the day and for six to ten hours during the night

Contraindications to the method are various types of rhinitis Even a simple coryza or cold may cause failure of absorption of the pituitary powder Anterior rhinoscopy at times may be of value as a preliminary to the administration of the extract

Rees and Olmsted[115] in 1932 found that desiccated posterior lobe substance in salol coated capsules taken orally controlled polydipsia and polyuria However when given by mouth without capsule the extract had no effect I have used tablets of pituitary extract by mouth in a number of cases without effect on diabetes insipidus

Reactions to Effects of Posterior Pituitary Extract —The separation of pitressin and pitocin from pituitary extract necessitated apportioning these multiple pharmacodynamic actions[116] Pitressin elicits the cardio

vascular the respiratory renal intestinal and certain metabolic effects whereas pitocin exerts the oxytocic action Both substances cause hyperglycemia and act as antagonists to insulin[2,3] Although solution of pituitary U S P or pitressin are said to be contraindicated in hypertension the therapeutic doses of either of these solutions given intramuscularly subcutaneously or intranasally do not cause any significant rise in blood pressure in man in spite of the resultant pallor of the patients

A brief fall in the pulse rate oxygen consumption and cardiac output is followed by a more prolonged rise[111] The decreased cardiac output after the injection of solution of the posterior pituitary or pitressin is due largely to a coronary constriction which may be obviated by administration of adrenalin or ephedrin[114]

Starr and associates[113] studying the action of pitressin in three cases of diabetes insipidus found no change in the cardiac output respiration metabolic rate and electrocardiograms in two cases On the other hand Melville[115] found pituitrin produced T wave changes which represented ventricular effects resultant from anoxemia secondary to coronary constriction

Resistance to Solution of Posterior Pituitary —The reported resistance to solution of posterior pituitary has not occurred in my patients although at times some of them required more pituitrin than others for the control of the polydipsia and polyuria Out of 74 cases of diabetes insipidus in the literature Fradiss[104] collected 1. cases which were refractory to pituitrin therapy In three instances antisyphilitic treatment was successful after the failure of the pituitrin

On the basis of two cases Biggart[106] suggested an anatomical lesion as a possible cause for resistance to the antidiuretic factor His first patient a 19 year old boy and an imbecile with paralysis agitans had a daily fluid intake of about 15 liters His second patient was a 43 year old man with recent diabetes insipidus who responded to pituitrin for two months and then became refractory Biggart believed that damage to the tuberal nuclei with or perhaps without concommitant damage to the supraoptic hypophyseal system resulted in a form of diabetes insipidus not controlled by the antidiuretic factor

However I do not believe that an anatomical basis per se is the cause of the resistance to pituitrin In diabetes insipidus the decreased reabsorption of water in the tubule of the kidney is restored to normal following the administration of pituitrin This condition would be expected to occur whether or not the tuberal nuclei are affected It appears more likely that in these refractory cases that there is present

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posterior pituitary and of pitressin appears to be somewhat more satisfactory because it avoids the necessity of injection and can be taken easily a number of times a day Again however the effect lasts only a few hours and frequently the irritation of the nasal membranes causes a diminished absorption

A compound solution of posterior pituitary with slow absorption and a greatly prolonged antidiuretic effect is desirable especially if there are no side reactions Pitressin tannate in oil administered hypodermically to patients with diabetes insipidus has been found to have an antidiuretic effect[illegible] which may last from 4 to 96 hours In 17 of my cases including eight published ones[illegible] 1 c c of pitressin tannate in oil was injected subcutaneously or intramuscularly daily for several days and then on alternate days or at longer intervals The dose has to be adjusted according to the requirements of the individual patient Some cases eventually required only ½ c c of pitressin tannate in oil every other day

All of the cases were of idiopathic origin except one with a brain tumor There were 12 males and 5 females Their ages ranged from 14 to 72 years All had had diabetes insipidus for a number of years and had been relieved of the polyuria and polydipsia with intramuscular or intranasal administration of solution of posterior pituitary except for the patient with the brain tumor Illustrations of the effect of this drug on the fluid intake and output are shown in Fig 2 and Fig 23

The hypodermic administration of 1 c c of pitressin tannate in oil was very effective in reducing the fluid intake and output to normal in these cases The effect of the first injection of the drug was so evident that the subsequent 24 hour fluid intake and urine volume were normal When injected daily its antidiuretic effect became cumulative and these volumes decreased to below the average normal The antidiuretic effect usually was as obvious during the second 24 hours as it was during the first 24 hours after the injection of the drug Consequently the frequency of the use of 1 c c of this medication was adjusted so that it was given every 48 or 60 hours With this adaptation the fluid intake was near normal and the polyuria polydipsia and thirst completely disappeared In the case of brain tumor the duration of action of the drug was only about 30 hours but in this case solution of posterior pituitary had no effect This was the only case in which the drug was needed daily At times there have been some ampules of the drug which did not have a maximum effect due to some difficulty in its manufacture

a neutralizing factor in the blood or that there is some variation in the resistance due to allergy to pituitrin Biggart's second case which responded to the pituitrin for the first two months and then became refractory would seem to substantiate this idea

Resistance to pituitrin in diabetes insipidus could be studied advantageously by using Lowell's methods in investigating insulin resistance Recently he[4 0] found certain variations in resistance and allergy to insulin and demonstrated that the blood contained a neutralizing factor exhibiting some characteristics of an antibody His findings indicated also that the allergy to insulin and the resistance to insulin varied independently of each other

In this connection Williams and Cole[4 04] reported a case with diabetes insipidus in which the injection of pitressin tannate in oil did not alter the urine volume but caused a chill with a temperature of 101 F within 30 minutes The intradermal injection of pitressin produced a violent local allergic reaction within 30 minutes Neither the serum nor the body cells were found to inactivate pitressin any more rapidly than in normal individuals They concluded that there is probably a congenital anomaly of the loop of henle and the distal convoluted tubules in this patient

Dancis and associates[463] reported a similar case of a 6-month old girl with congenital diabetes insipidus who was resistant to treatment with pitressin They believed that the polyuria was not due to a deficient neurohypophyseal activity because the polyuria did not respond to pitressin and because large amounts of an antidiuretic substance was present in this patient s urine They suggested that in this case the polyuria was due to a congenital anomaly of the kidney, possibly an end organ defect resulting in inability of the kidneys to respond to normal hormonal control

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Fig 22 Relative effects of pitressin pitressin tannate in oil and no treatment on the daily fluid intake and output of a patient (Mr H N) with diabetes insipidus

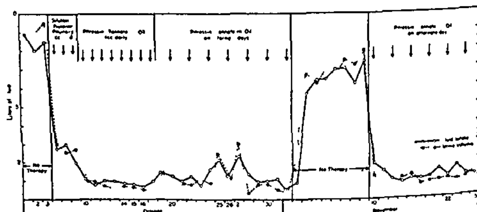


Fig 23 Relative effects of solution of posterior pituitary pitressin tannate in oil and no treatment on the daily fluid intake and output of a patient (Miss E.S) with diabetes insipidus

The patients themselves commented on the fact that pitressin tannate in oil increased their saliva and improved their appetite and digestion. Also the dryness in the mouth which occurred even with solution of posterior pituitary disappeared. There were no disagreeable side reactions such as local irritation, slough, pallor or intestinal cramps nor significant changes in the body weight.

In some cases I am using pitressin tannate in hydrogenated peanut oil (Parke Davis & Co) which is made up in a disposable syringe 1 c c in size and contains 5 units of pitressin. The duration of effect of 1 c c of this preparation is usually 5 or 6 days; in one patient the effect lasted 10 to 14 days. However, in some cases a local irritation occurred at the site of injection.

The hematocrit and phenolsulfonephthalein excretion were determined in one case before, during and after treatment with pitressin tannate in oil. The phenolsulfonephthalein excretion remained the same during the various periods of observation, being approximately 68 per cent in 130 minutes. The blood showed slight dilution as evidenced by the hematocrit of 4 per cent without treatment and 38 per cent during therapy.

The fluid intake and output of patients with diabetes insipidus was maintained at a normal level with pitressin tannate in oil more consistently and satisfactorily than with any other drug.

Other Methods of Treatment

As has already been stated at the beginning of this chapter, the successful treatment of the cause of diabetes insipidus is quite rare. However, when diabetes insipidus is associated with some other conditions, treatment of such a condition has resulted at times in an improvement or cure of the diabetes insipidus. Therapy has included surgery, x ray, lumbar puncture, treatment of infections, diet, drugs and other miscellaneous methods. Here again the results have varied. Some of the important findings will be summarized.

In the old literature a *variety of drugs* were used in an attempt to control the polyuria and polydipsia of diabetes insipidus, particularly because pituitary extract was not available then. A list of these drugs includes valerian, asafetida, ergot[4], nitroglycerin, digitalis, antipyretics such as amidopyrine (pyramidon)[4,6], antipyrine[4,7], salicylates and seda

tives such as opium bromides and phenobarbitol In general they had very little if any, practical effect Bromides and phenobarbitol have been used in order to enable the patient to sleep However, with present day treatment these drugs are really not necessary

Lumbar Puncture — Lumbar puncture has resulted in the disappearance of the polyuria and polydipsia in rare cases[436 437 438] One of my cases a 48-year old woman, with diabetes insipidus for 15 years improved temporarily following lumbar puncture The fluid intake and output dropped to two or three liters and returned to the original level of eight liters in nine days after lumbar puncture I have done lumbar punctures on many other cases of diabetes insipidus without any changes in fluid intake and output

Diet — Various forms of diet have been suggested for the treatment of diabetes insipidus including the low salt, low-protein and low calorie diets Allen and Sherrill[439] observed that restriction of protein and salt reduced thirst and polyuria in contrast to heavy protein feeding which increased these symptoms The restriction of the sodium chloride appeared more essential than the reduction of protein The best results were obtained when sodium chloride was limited to less than 1 gm daily However it is evident that marked curtailment in protein and salt are impractical because of their exhausting effect, particularly on the active patient Furthermore the resultant diminution in fluid intake and output is comparatively small and does not warrant such a regimen The same limitations are also true for the low-calorie diet

Treatment of Diabetes Insipidus in Combination with Other Diseases

Brain Tumor — Removal of certain brain tumors rarely results in a cure or in improvement of the polyuria and polydipsia A review of Cushing s cases at the Peter Bent Brigham Hospital reveals that removal of a brain tumor or evacuation of a cyst may produce no variations or may aggravate the diabetes insipidus in addition to effecting some improvement and causing a temporary or permanent cure No doubt the persistence of the diabetes insipidus after operation is due to the long continued pressure of the tumor, which damages the supraoptic hypophyseal system beyond regeneration Four of Cushing s cases developed post operative diabetes insipidus immediately after operation on craniopharyngeal pouch cysts Recently Grant[475] reported complete relief of diabetes insipidus by evacuating the cysts in three out of four cases of

craniopharyngioma On the contrary in two other instances diabetes insipidus was a consequence of such an operation

X ray therapy to the pituitary and hypothalamic regions may be of value in relieving the symptoms of this disease if the cause is a tumor which is radio sensitive and if the changes in the supraoptic hypophyseal tract are not beyond repair Jones[117] and Horrax[118] each found that diabetes insipidus was benefited in three tumor cases treated in this manner Weinstein and Spingarn[428] reported a case of diabetes insipidus following a middle ear infection which terminated after deep roentgen therapy to the pituitary region

Irradiation with roentgen rays of the area of the hypophysis in a case of diabetes insipidus and diabetes mellitus[429] caused no effect on the excretion of urine but it did increase the excretion of sugar

Xanthomatosis — Various forms of treatment have been recommended for xanthomatosis including diets low in fat[4] high in calcium and vitamin D as well as insulin injection thyroid and parathyroid extracts Except for x ray therapy they have had little or no effect on the xanthomatous process and diabetes insipidus Improvement in the xanthomatosis may result in amelioration of the polyuria and polydipsia However spontaneous remissions may occur in this disease as well as during any form of therapy[430, 431] The effect of x ray therapy in xanthomatosis seems to be local and specific Sosman[432] showed that there was a prompt disappearance of the defects in the bones but that the improvement was least marked with regard to the exophthalmos

Syphilis — Certain cases of diabetes insipidus associated with syphilis may respond to antisyphilitic treatment[43] In 1909 Ebstein[433] found that antisyphilitic treatment benefited 17 out of 23 cases of diabetes insipidus with syphilitic meningitis Benario[434] reported either a cure or improvement with arsphenamine therapy in seven cases Umber[435] cured with antisyphilitic treatment a patient whose Wassermann reaction was positive in the blood and negative in the spinal fluid Schnetz and Luchner[4] obtained successful results with malarial treatment of diabetes insipidus of syphilitic origin

One of our patients a 36 year old woman with diabetes insipidus and syphilis improved rapidly within two weeks after treatment with arsphenamine mercury succinimide and potassium iodide Another patient a 17 year old boy who had congenital syphilis and diabetes insipidus of two years duration was treated on many occasions for syphilis The Wassermann reaction remained positive and there was no improvement

in his diabetes insipidus He did not respond to pituitrin therapy However, autopsy revealed that this boy had two separate tumors one a tumor of the third ventricle and another an adenoma of the pineal gland

Cammidge s patient[139], a 42-year old man, with an old syphilis history and mild diabetes insipidus was given antisyphilitic treatment without benefit Yet the polyuria rapidly subsided after lumbar puncture The symptoms of diabetes insipidus probably were due to parasyphilitic changes at the base of the brain which interfered with the passage of secretion of the hypophysis into cerebrospinal fluid Withdrawal of some of the fluid by sudden changes of pressure produced within the cerebrospinal canal most likely broke down adhesions and opened a channel for its normal passage again to relieve the diabetes insipidus

Pellagra — Since polyuria and polydipsia are so frequent an accompaniment of pellagra, naturally cases of diabetes insipidus associated with pellagra should be treated as a deficiency disease with a high vitamin content in the diet especially nicotinic acid This form of therapy has been shown to improve the polyuria and polydipsia

Infections — When the origin of the disease is tuberculosis or encephalitis due to other infections these diseases should be viewed differently from the manner in which they were in the past With the modern methods of chemotherapy and antibiotics some of these cases that did not respond to treatment previously, possibly may respond now

Other Endocrine Treatment

There is a close relationship between diabetes insipidus and the general endocrine system Certain other endocrine treatment in addition to posterior pituitary therapy has been used in an attempt to relieve the symptoms of diabetes insipidus Other methods of endocrine therapy used in diabetes insipidus include transplantation of the pituitary gland thyroidectomy, the administration of thiouracil, antuitrin-S estrogens testicular extracts and corpus luteum extract

Transplantation of Pituitary Gland — Experimental work on the transplantation of the pituitary gland has been reported Hirsch and Demel[140] in 1936 implanted a human hypophysis in the abdomen of a patient with a resultant cure of the diabetes insipidus Hirsch[141] successfully transplanted into the rectus muscle of a patient with traumatic diabetes insipidus the posterior lobe of a human hypophysis obtained from a person of the same blood group but of different sex The polyuria

was much reduced In further experimental work Hirsch in 1937 grafted the pituitary gland of a sheep into a young patient with transitory relief

Azerad[111] implanted very small fragments of posterior pituitary gland of the bull in a female patient with diabetes insipidus and obtained complete relief of the polyuria and polydipsia within one half hour after the implantation This relief lasted 8 to 11 days on repeated occasions The fresh posterior lobe of the pituitary gland was cut into small particles mixed with physiological salt solution and then injected subcutaneously through a needle 1 mm in diameter He also had used the hypophysis of a premature human fetus delivered by caesarean section but obtained no improvement in the diabetes insipidus Apparently the embryo was too young

In the case of Falta and Titze[169] the polyuria was reduced only temporarily by the implantation of two calf hypophyses in the abdominal skin of the patient

Total Thyroidectomy in Diabetes Insipidus — Because the thyroid gland probably plays a role in the regulation of the intake and output of fluids in patients with diabetes insipidus it appeared of value to apply this knowledge clinically in the treatment of diabetes insipidus Consequently total thyroidectomy was performed in 1935 on three of my patients with this disease[9] aged 7 29 and 66 years They have been observed for the subsequent 13 years since thyroidectomy The etiology was idiopathic in one case and of postencephalitic origin in two cases

In the two cases of postencephalitic origin after total thyroidectomy there was a gradual decrease in the fluid intake and output This finding is illustrated in Fig on an earlier page In addition there was some beneficial effect on the Parkinson s disease Thyroidectomy had no appreciable effect on the diabetes insipidus of idiopathic origin The evidence in these cases justify the application of thyroidectomy in patients with diabetes insipidus associated with postencephalitic Parkinson s disease but not in the idiopathic type Since these patients had total thyroidectomies performed in 1935 several reports have appeared in the literature on total or subtotal thyroidectomy in patients with diabetes insipidus

McConnell[112] reported a case in which diabetes insipidus and thyrotoxicosis were associated with a thyroid adenoma and removal of the adenoma of the thyroid gland resulted in immediate relief of the symptoms of diabetes insipidus On the other hand McPhedran s[113] case of diabetes insipidus and toxic goiter showed no improvement in the polyuria after subtotal thyroidectomy Ferro Luzzi[114] and Findley[115] each

reported a case of diabetes insipidus in which total thyroidectomy had no appreciable effect on the polydipsia and polyuria of the disease There was no guarantee that all the thyroid tissue was removed However, both of their patients had syphilis which may have been a factor in their results

Thiouracil and Propylthiouracil in Diabetes Insipidus —Relief of polyuria in certain cases of diabetes insipidus following total thyroidectomy has led to the use of thiouracil and propylthiouracil Astwood[116] has demonstrated that thiouracil and propylthiouracil caused a marked reduction in the basal metabolic rate and relieved hyperthyroidism by action on the thyroid gland

In a group of four of my patients with diabetes insipidus the administration of thiouracil had no effect on the fluid intake and output in three ambulatory patients However, there was a marked decrease in one who was a 43-year old man with diabetes insipidus for many years He was treated in the hospital for five months The gradual reduction of his fluid volume after the administration of [illegible] gm thiouracil five times a day is shown in Fig 24 During this period of observation his basal metabolism fell from plus 6 per cent at the start of treatment to minus 10 per cent His thyroid gland became slightly enlarged There were no other marked changes Biopsy of the thyroid gland one and four months after the starting of thiouracil showed slight hyperplastic changes

A second patient in this group showed a striking change as a result of a similar administration of thiouracil While there was no decrease in his fluid intake and output the thyroid gland became considerably enlarged increasing his neck circumference by approximately two inches However omission of the drug restored his neck to its normal size in two months

Propylthiouracil 100 milligrams three times a day was given to four patients with diabetes insipidus for several months In these cases there was no appreciable change in the fluid intake and output even though the basal metabolism decreased

The appreciable effects which the thiouracil had on the first case may have been due to changes in the pituitary gland Reveno[117] found that the administration of thiouracil in animals caused the disappearance of the eosinophilic elements Furthermore the increased basophilia in the anterior lobe of the pituitary gland simulated changes found in those subjected to thyroidectomy where the development of so called "thyroidectomy cells" take place

Sex Hormones —Meyer-Noble[118] found corpus luteum extract to be

effective in relieving the polyuria and polydipsia in a girl with delayed menstruation

There is experimental evidence that the administration of estrogenic substance may suppress the diabetogenic and sex principles of the anterior lobe of the pituitary gland The polyuric effect of certain extracts of the anterior lobe of the pituitary has been reported by a number of authors[119, 40] and *it is believed that this gland secretes a diuretic substance* It seemed practical to determine whether the so-called diuretic principle of the anterior pituitary gland may be suppressed in a similar manner There have appeared clinical investigations to substantiate this idea Troisier[111] and Beltrametti[41] have injected large doses of folliculin into patients with diabetes insipidus and obtained a marked antidiuretic

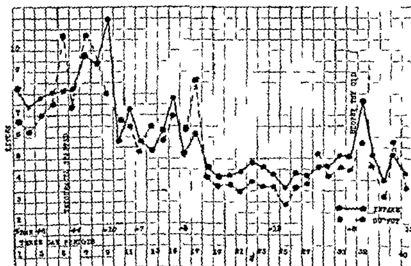


Fig 24 The effect of thiouracil 0.2 grams five times a day on the daily fluid intake and output of a patient in the hospital for four months Each observation period represents three days Patient had diabetes insipidus of idiopathic origin Thyroid *biopsy 5 months after starting thiouracil was again followed by temporary increase in* polyuria and polydipsia

effect within several days Omission of the folliculin resulted in a return of the polyuria Astwood[12] also noted following amniotin administration a temporary improvement of the diabetes insipidus in a woman in whom menopause had been induced artificially five years previously by

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insipidus which was permanently cured by an intercurrent attack of measles back in 189

Diabetes insipidus has disappeared even after the application of blisters to the chest[7]

Bee Stings — McPhedran[445] reported that a man was cured of diabetes insipidus following 40 bee stings received all at one time

In one patient with diabetes insipidus I injected bee venom (Lyovac Sharp and Dohme) the equivalent of 40 stings during a period of eight days This therapy resulted in no decrease in the fluid intake and output I did not dare to give 40 stings at one time because the patient was allergic

Electric Shock — Electric shock treatment in mental disorders has been used since 1938 Ellis and Wiersma[4] studied the influence of electronarcosis on the secretory activity of the pituitary gland in guinea pigs and dogs They found that electronarcosis in animals resulted in hypertrophy of the thyroid adrenals and gonads Since an increase in thyrotropic substance is found in the blood of electronarcotized dogs they believed that the mechanism by which thyroid hypertrophy is obtained is by an increased secretion of the pituitary hormone It is conceivable that general cortical and subcortical stimulation from passage of the current could produce direct nerve stimulation of respective endocrine organs

The effect of electric shock treatment was studied in one of my patients a 35 year old man with diabetes insipidus for over 16 years He was depressed and agitated and drank much liquor He was given 16 standard electric shock treatments in four weeks time During the subsequent nine months of observation there has been no improvement in the polyuria and polydipsia If anything there was a slight increase in the daily fluid intake and output

Short Wave Treatment — Drouet Verain Grandpierre and Pierquin[460] found that short wave treatment of the tubero pituitary region reduced the polyuria from seven to two liters in a case of traumatic diabetes insipidus Whether this is a matter of coincidence is a question because of the tendency to spontaneous improvement after traumatic diabetes insipidus

Surgery in Patients with Diabetes Insipidus

Surgery may be performed on patients with diabetes insipidus without any greater risk than in the general run of cases Preparation for

irradiation of the ovaries Shapiro[453] observed that the urine volume decreased 30 to 60 per cent after the injection of large doses of estrogen (oestradiol benzoate, 10 mgm daily for five days) in normal persons and in those with diabetes insipidus After the omission of the drug the urine volume returned to its pre-injection level On the basis of the fact that pregnancy improved diabetes insipidus in a patient Duvoir, Pollet and Cachin[331] administered folliculin to this patient and obtained a reduction in the volume of urine again

I[44] treated five cases of diabetes insipidus with daily injections of 20 000 units of amniotin, the estrogenic substance prepared from the urine of pregnant mares and amniotic fluid, and found no change in their fluid intake and output Apparently this substance did not suppress the diuretic principle of the anterior lobe of the pituitary gland However there appeared a definite improvement in the sugar tolerance Such improvement has been noted by Barnes, Regan and Nelson[400] in experimental diabetes mellitus following the administration of amniotin Collens and associates[46], however were unable to confirm this change

Allen and Stokes[81] reported a cure of diabetes insipidus coincident with bilateral correction of abdominal cryptorchidism in a boy following a series of 25 injections of 1 c c doses of antuitrin S during a two month period At the end of a month after the fifteenth injection the polyuria and polydipsia had disappeared

The injection of antuitrin-S over a period of two months in four of my cases caused no improvement in the symptoms of diabetes insipidus Antuitrin-S is the standard gonadotrophic factor of the anterior pituitary-like sex hormone obtained from the urine of pregnancy

Miscellaneous Treatment

There are reported instances in which the polyuria and polydipsia have terminated spontaneously Of the numerous cases of diabetes insipidus which I have followed for many years I have never seen a case of real diabetes insipidus terminate spontaneously However, there are cases in which intercurrent pathological conditions have caused patients to be relieved of the diabetes insipidus For example, Strauss[88] had a case of diabetes insipidus which disappeared with the appearance of myxedema Silvestri's[4] patient, a 20 year old youth was relieved of diabetes insipidus when his testes descended The polyuria had been present since the boy was four years old Harvey[18] presented a case of diabetes

edge of the cause and mechanism of the disease and more particularly antedate ability to manufacture the agent required to control diabetes insipidus in a form safe to give to man in a way effective in its control With these attained all of these other forms of treatment have become almost entirely obsolete and except for historical purposes largely may be forgotten

Now that we know that diabetes insipidus in the words of its definition as given on the opening page of this chapter is due to a deficient formation of pituitary extract secreted by the posterior lobe of the pituitary all that was necessary for adequate therapy was a knowledge of how to prepare such an extract from an available source in a form safe to give to man without losing its physiological activity With this accomplished by the preparation of posterior pituitary extract and pitressin treatment has become reduced to the use of these preparations as described under the heading Treatment Using them diabetes insipidus can be controlled so that no longer is it a menace to health and hardly more than a minor discomfort although in an accurate sense it is not a curable disease but only one that can be safely comfortably and almost completely controlled All the physician who has a patient with diabetes insipidus really needs to know so far as control of the diabetes insipidus itself is concerned is how to use posterior pituitary extract and/or pitressin Other methods therein discussed practically need never be used There are but few diseases at present whose treatment is so simple and so satisfactory as is true of diabetes insipidus

operation should be made according to the standard methods However, it is well to give patients pituitrin before operation to control water excretion Otherwise such individuals may become markedly dehydrated Furthermore, if no pituitrin is given, the bladder may become markedly distended with urine Local, spinal or general anesthesia may be used to fit the individual case

The type of surgery performed in most of my cases has been mainly for brain tumor because of the large group of such cases in this series It is surprising how well, in general, these patients went through the operations Three patients had operations for acute appendicitis and recovered Four had thyroid operations for therapy and study

One 54 year old woman had an abdominal perineal resection for an adenocarcinoma of the rectum She had a normal postoperative course until the seventeenth day when she died suddenly of a pulmonary embolus Another 63-year old woman had a panhysterectomy for adeno carcinoma of the fundus of the uterus with extension to the mesosalpynx and died several days later apparently of cerebral thrombosis A third patient 48 years old who had diabetes insipidus for 37 years had a hysterectomy for fibroids and made a rapid recovery after surgery

There were also other types of surgery including deliveries - cesarian operation minor operations and extractions of teeth without any difficulty Several patients had fractures due to trauma These healed normally

Diabetes insipidus is no contraindication to surgery and to the various forms and methods of anesthesia

Tonsillectomy —Winter[10] noted sudden recovery from diabetes insipidus in a 7-year old boy the day following tonsillectomy which was done under ether anesthesia In this case the child had had diabetes insipidus for 5 months previously and a daily fluid intake of 5760 c c which responded to pituitrin therapy There was no recurrence of the polyuria and polydipsia during the following year of observation It was felt that this boy had a chronic upper respiratory infection

Summary of Treatment

The treatment of diabetes insipidus illustrates almost perfectly the axiom that a multitude of remedies points to a woeful absence of knowledge of the cause and cure of a disease In the preceding pages a very large number of measures used in the past in the treatment of diabetes insipidus have been discussed Largely they antedate accurate knowl

10 KAHLER O Die Dauernde Polyurie als Cerebrales Herdsymptom Zeitschr f Heilk VII 105 1886
11 BAILEY P and BREMER F Experimental diabetes insipidus Arch Int Med 1921 XXVIII 773
12 MEYER E Über Diabetes insipidus und andere Polyurien Deutsch Arch f klin Med 1905 LXXXIII 1 TALLQUIST T W Untersuchungen uber einen Fall von Diabetes insipidus Zeitsch f klin Med 1903 IL 181 SOCIN CH Ueber Diabetes insipidus Zeitsch f klin Med 1913 LXXVIII 294
13 FINKELNBURG R Über das Konzentrationsvermogen der Niere bei Diabetes insipidus nach organischen Hirnerkrankungen Deutsch Arch f klin Med 1910 C 33 FITZ R A case of diabetes insipidus Arch Int Med 1914 XIV 706
14 MAGNUS R and SCHAFER F A The action of pituitary extracts upon the kidney Jour Physiol, 1901 XXVII Proceedings p IX
15 SCHAFER E A and HERRING P T The action of pituitary extracts upon the kidney Proceedings Roy Soc London 1905-06 Series B LXXVII 571
16 FRANK Ueber Diabetes insipidus als Zeichen gesteigerte Funktion des Hinterlappen der Hypophysis Berlin klin Wochnschr 1910 XLVII 1 57
17 FUTCHER T B The etiology and treatment of diabetes insipidus Ann Int Med 1931 32 V 566
18 GOETSCH E CUSHING H and JACOBSON C Carbohydrate tolerance and the posterior lobe of the hypophysis cerebri Bull Johns Hopkins Hosp 1911 XXII 165
19 CUSHING H Concerning diabetes insipidus and the polyurias of hypophyseal origin Boston Med and Surg Jour 1913 CLXVIII 901
20 FRANK E Ueber Beziehungen Hypophyse zum Diabetes insipidus Berlin klin Wochnschr 1912 XLIX 393
21 SIMMONDS M Ueber sekundare Geschwulste des Hirnanhangs und ihre Beziehungen zum Diabetes insipidus Munchen med Wochnschr 1914 LXI 180
22 von den VELDEN R Die Nierenwirkung von Hypophysenextrakten beim Menschen Berlin klin Wochnschr 1913 L 083
23 FARINI A Hypophyseal opotherapy in diabetes insipidus Gazz d Osp 1913 XXXIV 1135 abstracted Brit Med Jour 1913 II 76
24 CAMUS J and ROUSSY G Hypophysectomie et polyurie experimentales Compt rend Soc de biol 1913 LXXV 483 Diabete insipide experimental et opotherapie hypophysaire *ibid* 1920 LXXXIII 1578 Experimental researches on the pituitary body

BIBLIOGRAPHY

1 GALEN C Claudii Galeni Opera Omnia Editionem Curavit D C G Kuhn VIII 394, Lipsiae, Prostat in Officina Libraria Car Cnoblochii 1824

2 ARETAEUS THE CAPPADOCIAN The Extant Works of Aretaeus the Cappadocian Edited and Translated by Francis Adams London The Sydenham Society Book II Chapter II p 339 printed by Wertheimer and Co London 1856

3 WILLIS SIR THOMAS Pharmaceutice Rationalis sive Diatriba de Medicamentorum Operationibus in Humano Corpore Sectio IV Caput III De Diuresinima eiusque remedio & speciatim de Diabete Hagae Comitis Ex Officina Arnaldi Leers Bibliopolae p 172 1674 Pharmaceutice Rationalis sive Diatriba de Medicamentorum Operationibus in Humano Corpore Sectio IV Caput III de Diuresinima eiusque remedio & speciatim de Diabete p 67 Amsterdam Apud Henricum Weststenium Dr Willis's Practice of Physick being the whole WORKS of that Renowned and Famous Physician Section on Pharmaceutice Rationalis Part I, p 71 London printed for T Dring C Harper and F Leigh 1684

4 CULLEN, W Ansfangsgrunde der praktischen Arzneykunst p 566 Caspar Fritsch Dritter Band Leipsig 1789

5 BELLOT M M and BROUGNIART Report made to the Philomatical Society relative to a woman who drinks a great quantity of water in Simmons's Medical Facts and Observations II 87 J Johnson London 1792

6 FRANK JOHANN PETER Grundsatze uber die Behandlung der Krankheiten des Menschen zu akademischen Vorlesungen bestimmt Funfter Theil von den Ausflussen (Profluvia) Mannheim Schwan und Goss p 34 1797 I Ordnung II Geschlecht Harnruhr FRANK JOANNE PETRO De Curandis Hominum Morbis Epitome Praelectionibus Academicis Dictata Classio Quinta Profluvia Florentiae Apud Coen et Socios 1832 Ordo I, Genus II p 25

7 WILLIS ROBERT Urinary diseases and their treatment Sherwood Gilbert and Piper London 1838 p 2

8 BERNARD C Leçons de Physiologie Experimentale Tome 1 Leçon Dix Huitieme, p 345, 27 Fevrier 1855 J B Baillière et Fils Paris 1855

9 ECKHARD C Die Stellung der Nerven beim kunstlichen Diabetes Beiträg z Anatomie u Physiologie 1869 IV 1 Untersuchungen uber Hydrurie *Ibid* 1869 IV 153 Untersuchungen uber Hydrurie *Ibid*, 1870 V 147 Untersuchungen uber Hydrurie *Ibid*, 187 VI 51

Physiol 1935 CXII 481 Experimental diabetes insipidus its relation to the anterior and posterior lobes of the pituitary Am Jour Physiol 1934 CX 124

37a BELLOWS R T and Van WAGENEN W P The relationship of polyuria and polydipsia in diabetes insipidus a study of experimental diabetes insipidus in dogs with and without esophageal fistulae Jour Nervous and Mental Disease 1938 LXXXVIII 417

38 GREINAR A and PODHRADSZKY L Kidney function in diabetes insipidus Lancet 1947 II 498 SAMAAN A The effect of the pituitary (posterior lobe) extract upon the urinary flow in non anesthetized dogs Jour Physiol 1935 LXXXV 37 HANDOVSKY H and SAMAAN A Effet des extraits posthypophysaires sur le debit sanguin renal et sur la diurese des chiens narcotises Compt rend Soc de Biol 1936 CXXII 1 2 Observations on the renal circulation and secretion in the dog with special reference to the effect of pituitary (posterior lobe) extract Jour Physiol 1937 LXXXIX 14

39 SCHMITZ H L The mechanism of human diabetes insipidus Jour Clin Invest 1937 XVI 675

40 WHITE H L and HEINBECKER P Hypophyseal influences in renal function and water exchange in the dog Am Jour Physiol 1938 CXXIII 13 Observations on inulin and diodrast clearances and on renal plasma flow in normal and hypophysectomized dogs Am Jour Physiol 1940 CXXX 464 Observations on creatinine and urea clearances on responses to water ingestion and on concentrating power of kidneys in normal diabetes insipidus and hypophysectomized dogs Am Jour Physiol 1938 CXXIII 566 WHITE H L HEINBECKER P and ROLF D Effects of hypophysectomy on some renal functions Proceed Soc Exper Biol and Med 1941 XLVI 44

41 WINER N J Renal function in diabetes insipidus Arch Int Med 194 LXX 61

42 STARLING E H and VERNEY E B The secretion of urine as studied on the isolated kidney Proceed Roy Soc London s B 19 5 XCVII 3 1

43 JANSSEN S Ueber zentrale Wasserregulation und Hypophysen antidiurese Arch f exper Path u Pharmakol 19 8 CXXXV 1

44 VERNEY E B The secretion of pituitrin in mammals as shown by perfusion of the isolated kidney of the dog Proceed Roy Soc London s B 19 6 XCIX 487 Die Wasserausscheidung der Saugetierniere und ihre physiologische Regulation Arch f exper Path u Pharmakol 1936 CLXXXI 3 KLISIECKI A PICKFORD M ROTHSCHILD P and VERNEY E P The absorp

Diabetes insipidus glycosuria and those dystrophies considered as hypophyseal in origin Endocrinology 1920 IV, 507
25 ERDHEIM J Ueber Hypophysengangsgeschwulste und Hirncholesteotome Sitzungsb d k akad d Wissensch Math naturw Cl, 1904 CXIII 537
26 CHRISTIAN H A Defects in membranous bones Exophthalmos and diabetes insipidus, an unusual syndrome of dyspituitrism a clinical study in Contributions to medical and biological research I 391 Dedicated to Sir William Osler, Paul B Hoeber New York 1919
27 ELMER A W KEDZIERSKI J and SCHEPS M Ein Fall von Diabetes insipidus verursacht eine Metastase eines Hypernephrons im Zwischenhirn Beitrag zur Pathogenese des Diabetes insipidus Wien klin Wochnschr, 1928, XLI 591
28 GREVING R Beitrage zur Anatomie der Hypophyse und ihren Funktion 1 Eine Faserverbindung zwischen Hypophyse und Zwischenhirnbasis (Tr supraoptico hypophyseus) Deutsch Zeitschr f Nervenh 1926, LXXXIX 179
29 PINES I L Über die Innervation der Hypophysis cerebri II Mitt Ueber die Innervation des Mittel und Hinterlappens der Hypophyse Zeitschr f d ges Neurol u Psychol 1925-26 C 123
30 ZADEK E Die Beziehungen zwischen Anatomie und Klinik des Diabetes insipidus Zeitschr f klin Med, 19 7 CV 603
31 BLOTNER H and CUTLER E C Total thyroidectomy in the treatment of diabetes insipidus Jour Am Med Assoc 1941, CXVI 2739
32 ROGOWITSCH N Die Veranderungen der Hypophyse nach Entfernung der Schilddruse Beitrag z. path Anat u z allg Path 1889 IV 453
33 FISHER C INGRAM W R and RANSON S W Diabetes insipidus and the neuro-hormonal control of water balance, a contribution to the structure and function of the hypothalamico hypophyseal system Edwards Brothers Inc Ann Harbor Michigan 1938
34 FRIEDGOOD H B Endocrine functions of the hypophysis p 811 Oxford Medicine Vol III chapt XIV Oxford University Press Inc New York 1945
35 CANNON W B The physiological basis of thirst Proceed Roy Soc London s B 1917 18 XC 283 Hunger and Thirst Murchison s Psychology Clark University Press Worcester Mass 1934
36 HOLMES J H and GREGERSEN M I Origin of thirst in diabetes insipidus Am Jour Med 1948 IV 503
37 RICHTER C P Experimental diabetes insipidus Brain 1930 LIII 76 The primacy of polyuria in diabetes insipidus Am Jour

Physiol 1933 CVII 481 Experimental diabetes insipidus its relation to the anterior and posterior lobes of the pituitary Am Jour Physiol 1934, CX 1-4

37a BELLOWS R T and Van WAGENEN W P The relationship of polyuria and polydipsia in diabetes insipidus a study of experimental diabetes insipidus in dogs with and without esophageal fistulae Jour Nervous and Mental Disease 1938 LXXXVIII 417

38 GREINAR A and PODHRADSZKY L Kidney function in diabetes insipidus Lancet 1947 II 498 SAMAAN A The effect of the pituitary (posterior lobe) extract upon the urinary flow in non anesthetized dogs Jour Physiol 1935 LXXXV 37 HANDOVSKY H and SAMAAN A Effet des extraits posthypophysaires sur le debit sanguin renal et sur la diurese des chiens narcotises Compt rend Soc de Biol 1936 CXXII 1 2 Observations on the renal circulation and secretion in the dog with special reference to the effect of pituitary (posterior lobe) extract Jour Physiol 1937 LXXXIX 14

39 SCHMITZ, H I The mechanism of human diabetes insipidus Jour Clin Invest 1937 XVI 675

40 WHITE H L and HEINBECKER P Hypophyseal influences in renal function and water exchange in the dog Am Jour Physiol 1938 CXXIII 213 Observations on inulin and diodrast clearances and on renal plasma flow in normal and hypophysectomized dogs Am Jour Physiol 1940 CXXX 464 Observations on creatinine and urea clearances on responses to water ingestion and on concentrating power of kidneys in normal diabetes insipidus and hypophysectomized dogs Am Jour Physiol 1938 CXXIII 566 WHITE, H L HEINBECKER P and ROLF D Effects of hypophysectomy on some renal functions Proceed Soc Exper Biol and Med 1941 XLVI 44

41 WINER N J Renal function in diabetes insipidus Arch Int Med 1942 LXX 61

42 STARLING E H and VERNEY E B The secretion of urine as studied on the isolated kidney Proceed Roy Soc London s B 19 5 XCVII 3 1

43 JANSSEN S Ueber zentrale Wasserregulation und Hypophysen antidiurese Arch f exper Path u Pharmakol 1928 CXXXV 1

44 VERNEY E B The secretion of pituitrin in mammals as shown by perfusion of the isolated kidney of the dog Proceed Roy Soc London s B 19 6 XCIX 487 Die Wasserausscheidung der Saugetierniere und ihre physiologische Regulation Arch f exper Path u Pharmakol 1936 CLXXXI 3 KLISIECKI A PICKFORD M ROTHSCHILD P and VERNEY E P The absorp

tion and excretion of water by the mammal the relation between absorption of water and its excretion by the innervated and denervated dog Proceed Roy Soc London s B 1933 CXII 496 THEOBALD, G W The repetition of certain experiments on which Molitor and Pick base their water centre hypothesis and the effect of afferent nerve stimuli on water diuresis, Jour Physiol 1934 CCXLIII 81

45 ADDIS T SHEVKY A F and BEVIER, G The regulation of renal activity VII The balance between the regulation of adrenalin and by pituitrin Am Jour Physiol, 1918 XLVI 1 9

46 POULSSON, L T Ueber die Wirkung des Pituitrins auf die Wasserausscheidung durch die Niere Zeitschr f d ges exper Med 1930 LXXI 577

47 GERSCH I and STIEGLITZ E J Histochemical studies of the mammalian kidney 1 The glomerular elimination of ferrocyanide in the rabbit and some related problems Anat Rec 1934 LVIII 349

48 GERSCH, I Reabsorption of water during pituitary anti diuresis Jour Pharmacol and Exper Therap 1934 LII 231

49 BURGESS W W HARVEY A M and MARSHALL E K Jr The site of antidiuretic action of pituitary extract Jour Pharmacol and Exper Therap 1933 XLIX 237

50 Van DYKE H B The Physiology and Pharmacology of the Pituitary Body The University of Chicago Press Chicago Illinois 1936

51 STEHLE R L The constituent of the posterior lobe of the pituitary gland responsible for the antidiuretic action Jour Pharmacol and Exper Therap 1934 LI 146 Der antidiuretisch wirkende Anteil des Hypophysenhinterlappens Arch f exper Path u Pharm 1934 CLXXV 466

52 GEILING E M K The posterior hypophysis Jour Am Med Assoc, 1935 CIV 738

53 GERSCH I The structure and function of the parenchymatous glandular cells in the neurohypophysis of the rat Am Jour Anat 1939 LXIV 407

54 BROOKS C McC and GERSCH I Pericellular nerve terminations in the pars nervosa and pars distalis of the rat s pituitary Anat Rec 1938 LXX (Suppl 3) 10

55 GEILING E M K and LEWIS M R Further information regarding the melanophore hormone of the hypophysis cerebri Am Jour Physiol 1935 CXIII 534

56 VERNEY E B The secretion of pituitrin in mammals as shown by perfusion of the isolated kidney in the dog Proceed Roy Soc London 1926 XCIX 487 Goulstonian lectures on polyuria I

Polyuria associated with pituitary dysfunction Lancet 1929 CCXVI 539
57 VERNEY E B Absorption and excretion of water The antidiuretic hormone The Lancet 1946 Nov 3 (p 739) and Nov 30 (p 781)
57a VERNEY E B The antidiuretic hormone and the factors which determine its release Proceed Roy Soc B 1947 CXXXV 5
58 KLISIECKI A PICKFORD M ROTHSCHILD P and VERNEY E P The absorption and excretion of water by the mammal the relation between absorption of water and its excretion by the innervated and denervated dogs Proceed Roy Soc London s P 1933 CXII 496
59 GILMAN A and GOODMAN I Secretion of antidiuretic hypophyseal hormone in response to the need for renal water conservation Science 1936 LXXXIV 4 The secretory response of the posterior pituitary to the need for water conservation Jour Physiol 1937 XC, 113
60 SHANNON J A The control of the renal excretion of water The rate of liberation of the posterior pituitary antidiuretic hormone in the dog Jour Exper Med 194 LXXVI 387
61 VON HANN F Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus Frankf Zeitschr f Path 1918 XXI 337
61a HIRSCH O Diabetes insipidus Wien klin Wochnschr 1931 XLIV 1387 Personal communication
62 CUSHING H Concerning diabetes insipidus and the polyurias of hypophyseal origin Boston Med and Surg Jour 1913 CLXVIII 901 RICHTER C P Experimental diabetes insipidus its relation to the anterior and posterior lobes of the hypophysis Am Jour Physiol 1934 CX 439 PENCHARZ R I HOPPER J Jr and RYNEARSON E H Water metabolism of the rat following removal of the anterior lobe of the hypophysis Proceed Soc Exper Biol and Med 1936 XXXIV 14
63 KELLER A D Hypophyseal thyrotropic mechanism essential for occurrence of diabetes insipidus in its maximal force Proceed Soc Exper Biol and Med 1937 XXXVI 787
64 BEST C H and TAYLOR N B The Physiological Basis of Medical Practice p 740 The Williams and Wilkins Company Baltimore 1945
65 RICHTER C P and WISLOCKI G B Anatomical and behavior changes produced in the rat by complete and partial extirpation of the pituitary gland Am Jour Physiol 1930 XCV 481

66 TEEL H M and CUSHING H Studies on the physiological properties of the growth promoting extracts in the anterior hypophysis Endocrinology 1930 XIV 157 TEEL H M Diuresis in dogs from neutralized alkaline extracts of the anterior hypophysis, Jour Am Med Assoc 19 9 XCIII 760
67 BARNES B O REGAN J F and BUENO J G Is there a specific diuretic hormone in the anterior pituitary Am Jour Physiol., 1933 CV 559 BIASOTTI, A Thyroide et action diuretique de l extrait antehypophysaire Compt rend Soc de Biol 1934, CXV 3 9 GAEBLER O H Some effects of anterior pituitary extracts on nitrogen metabolism water balance and energy metabolism, Jour Exper Med 1933 LVII 349 WHITE, H L and HEINBECKER P Pituitary regulation of water exchange in the dog and monkey Am Jour Physiol 1937 CXVIII 276
67a HARRIS G W Neural control of the pituitary gland Phys Reviews 1948 XXVIII 139
68 HOFMEISTER F Zur Physiologie der Schilddruse Fortschr d Med 189 X 81
69 GLEY E Recherches sur fonction de la glande thyroide Arch de Physiol 189 XXIV 311
70 PISENTI G and VIOLA G Beitrag zur normalen und pathologischen Histologie der Hypophyse und bezuglich der Verhaltnisse zwischen Hirnanhand und Schilddruse Centralbl f die med Wissensch 1890 XXVIII 450
71 SCHÖNEMANN A Hypophysis und thyroidea, Virchow s Arch f path Anat 1892 CXXIX 310
7 HERRING P T The effects of thyroidectomy on the mammalian pituitary Quart Jour Exper Physiol 1908 I 81
73 CORONEDI G Recherches comparatives sur l action des dieuretiques et de l extrait thyreoïdien sur le rein du chien thyreoidectomise Arch ital de Biol 1909 LII 336
74 BARNES B O REGAN J F and BUENO J G Is there a specific diuretic hormone in the anterior pituitary Am Jour Physiol., 1933 CV 559
75 BIASOTTI A Tiroides y accion diuretica del extract de lobulo anterior de la hipofisis Rev Soc Argent de Biol 1933 IX 409
76 MARINE, D and ROSEN S H Cited by Marine MARINE, D The physiology and principal interrelations of the thyroid Jour Am Med Assoc 1935 CIV 2 50
77 MAHONEY W and SHEEHAN D The effects of total thyroidectomy on experimental diabetes insipidus in dogs Am Jour Physiol 1935 CXII 50 FISHER C and INGRAM W R

Effect of feeding of thyroid or salt and thyroidectomy on fluid exchange of cats with diabetes insipidus Arch Int Med 1936 LVIII 117

78 STRAUSS I Uebergang eines Falles von Diabetes insipidus in Myxodem Deutsch med Wochnschr 19 0 XLVI 939

79 BLOTNER H and CUTLER L C Total thyroidectomy in the treatment of diabetes insipidus Jour Am Med Assoc 1941 CXVI 739

80 DEL CASTILLO E B and PASQUALINI R Q Diabetes insipida en el curso del ambarazo y despues de las castracion Medicina Buenos Aires 194 II 335

81 ALLEN A A and STOKES J S Cure of diabetes insipidus co incident with bilateral correction of abdominal cryptorchidism by gonadotropic factor from pregnancy urine Jour Am Med Assoc 1936 CVI 780

8 SCHLOTTHAUER C F Diabetes insipidus in a bovine male Jour Am Vet Med Assoc 1935 LXXXIX 673

83 HAMILTON J B Personal communication

84 GOTTLIEB K Die Pathologie der Dystrophia adiposogenitalis Ergebn d allgem Path u path Anat 19 1 XIX 575

85 LICKINT F Ist der Diabetes insipidus eine genitohypophysare Erkrankung Deutsch med Wochnschr 1934 LX 167

86 ROTHMANN H Zur Behandlungen des Diabetes insipidus mit Hodenextrakt Med Klin 19 5 XXI 1537

87 KAIRIUKSTIS V Organtherapie bei Diabetes insipidus Med Klin 19 5 XXI 1136

88 INGRAM W R and WINTER C A The effects of adrenalectomy upon the water exchange of cats with diabetes insipidus Am Jour Physiol 1938 CXXII 143

89 RAGAN C FERREBEE J W PHYFE P ATCHLEY D W and LOEB R F A syndrome of polydipsia and polyuria induced in normal animals by desoxycorticosterone acetate Am Jour Physiol 1940 CXXXI 73

90 SILVETTE H and BRITTON S W Renal function in oppossum and mechanism of cortico adrenal and post pituitary action Am Jour Physiol 1938 CXXIII 630 Theory of cortico adrenal and post pituitary influence on kidney Science 1938 LXXXVIII 150 BRITTON S W and COREY E L Antagonistic adrenal and pituitary effects on body salts and water Science 1941 XCIII 405 COREY E L and BRITTON S W Antagonistic action of desoxycorticosterone and post pituitary extract on chloride and water balance Am Jour Physiol 1941 CXXXIII 511

91 MULINOS M G SPINGARN C L and LOJKIN M E Diabetes insipidus like conditions produced by small doses of desoxycorticosterone acetate in dogs Am Jour Physiol 1941, CXXXV 10
92 WINTER C A and INGRAM W R Observations on the polyuria produced by desoxycorticosterone acetate Am Jour Physiol 1943 CXXXIX 710
93 ANDERSON J A and MURLIN W R Antagonism of pitressin and adrenal cortical extract in human diabetes insipidus Jour Pediatrics 194 XXI 326
94 SHELLING D H The Parathyroids in Health and Disease p 9 C V Mosby Company St Louis 1935
95 HARE K Water metabolism neurogenic factors in the hypothalamus and central levels of autonomic functions Proceed Assoc Research in Nervous and Mental Disease Res Publ Assoc Nerv Ment Dis Williams & Wilkins Co Baltimore 1940 XX 416
GERSCH I Water metabolism endocrine factors Ibid p 436
BARBOUR H G Hypothalamic control of water movement in response to environmental temperature Ibid p 449
96 STALMMLER M Diabetes insipidus und Hypophyse Ergebn d allgem Path u path Anat 193- XXVI 59
97 FULTON J F Harvey Cushing a Biography p 366 Charles C. Thomas Springfield Illinois 1946
98 BERBLINGER W Diabetes insipidus und Tumor in der Hypophyse Verhandl d deutsch path Ges 1913 XVI 27
99 GIERKE E von Hypophysis und Epiphysis bei diabetes insipidus Verhandl d deutsch path Ges 1914 XVII 200
100 SEKIGUCHI S Hypophyseal disorder in mammary cancer and its relation to diabetes insipidus Ann Surg 1916 LXIII 97
101 MARAÑON G Diabetes insipidus as a hypopituitary syndrome Endocrinology 19 1 V 159
102 TAKAO T Zur Frage des Zwischenhirn Hypophysenproblems Virchow s Arch f path Anat 1926 CCLXII 1 4
103 KARY C Pathologische anatomische und experimentelle Untersuchungen zur Frage des Diabetes insipidus Virchow s Arch f path Anat 1924 CCLII 734
104 PINES I L Ueber die Innervation der Hypophysis cerebri J f Psychol u Neurol 19 5 XXXII 80
105 GREVING R Beitrag zur Innervation der Hypophyse Klin Wochnschr 19 5 IV -181
106 KIYONO H Ueber Zwischenhirnveranderungen bei Diabetes insipidus Virchow s Arch f path Anat 19 5 CCLVII 477

107 FUTCHER T B Diabetes insipidus and lesions of the midbrain Report of a case due to metastatic tumor of the hypothalamus Am Jour Med Sci 19 9 CLXXVIII 837
108 DeSANTO D A So called functional hypopituitarism pathologic findings and report of a case Arch Neurol and Psychiat 1934 XXXI 134
109 BIGGART J H Diabetes insipidus Brain LVIII 86 Diabetes insipidus The site of formation of the antidiuretic hormone Edinburgh Med Jour 1936 XLIII 417
110 STRINGER S W Diabetes insipidus associated with pinealoma transplant in the tuber cinereum Yale Jour Biol and Med 1934 VI 375 FRIEDMAN E D and PLAUT A Tumor of the pineal gland (pinealocytoma) with meningeal and neural metastases Arch Neurol and Psychiat 1935 XXXIII 1324 DAVISON C and SELBY N E Hypothermia in cases of hypothalamic lesions Arch Neurol and Psychiat 1935 XXXIII 570
111 FINK E B Diabetes insipidus A clinical review and analysis of necropsy reports Arch Path 19 8 VI 10 A case of diabetes insipidus associated with syphilis of the hypophysis Endocrinology 19 6 X 317
11 BERNARD C Leçons sur les propietes physiologiques et les alterations pathologiques des liquides de l organisme vol Paris 1859
113 CAMUS J and ROUSSY G Diabete insipide et polyurie dite hypophysaire Presse med 1914 XXII 517 Experimental researches on the pituitary body Endocrinology 19 0 IV 507
114 PARSONS R J The pituitary gland and its relation to age hypertension and pathological processes a study of 107 unselected pituitaries p 366 Medical papers dedicated to Henry Asbury Christian Waverly Press Inc Baltimore 1936
115 CUSHING H and MARTIN P Primary gliomas of chiasm and optic nerves in their intracranial portion Arch Ophth 19 3 I II 209
116 MARTIN J and DAVIS L Syndrome of destruction of the pineal gland experimental and clinical observations Arch Int Med 1941 LXVII 1119
116a HORRAX G and WYATT J P Ectopic pinealomas in chiasmal region report of three cases Jour Neurol 1947 IV 309
116b HORRAX G The role of pinealomas in the causation of diabetes insipidus Ann Surg 1947 CXXVI 7 5
117 JONES C M Diabetes insipidus Clinical observations in 4 cases Arch Int Med 1944 LXXIV 81

118 NONNE M Hypophysiserkrankungen Munch med Wochnschr 1916 LXIII, 835 Syphilis und Nervensystem p -41, S Karger Berlin 1915
119 ROSENBLOOM J Control of polyuria in a case of diabetes insipidus by means of hypophyseal extract Jour Am Med Assoc 1918 LXX 1 9-
120a VON HOESSLIN R Tumor der Epiphysis cerebri Diabetes insipidus Oculomotoriuskernlahmung, Munch med Wochnschr 1896 XLIII, 9-
120b WENTZLER E Ein Fall von Carcinom der Hypophyse bei 9-jahrigem Knaben Monatschr f Kinderh 1937 LXIX 86
121 MOFFETT R D Craniopharyngeal pouch cyst arising from pituitary body operation with recovery Am Jour Dis Child 19 6 XXXII 89
122 CUSHING H Pituitary Body and its Disorders J P Lippincott Co, Philadelphia 191 Papers Relating to the Pituitary Body Hypothalamus and Parasympathetic Nervous System Charles C Thomas Springfield Illinois 193
1-3 DESBUQUOIS G Sur un cas de lymphogranulamatose maligne compliquee de diabete insipide Bull et Mem Soc med d Hop de Paris 1935 LI 1355
124 OPPENHEIM In Nothnagel Die Syphilitischen erkrankungen des Gehirns Speziellen Pathologie und Therapie Vienna 1896 IX 53
1 5 DROUET P L and HAMEL Diabete insipide chez un heredo syphilitique Rev med de l Est 1931, LIX, 661
1 6 DEMME Ein Fall von Diabetes insipidus abstracted Jahrb f Kinderh 1879 XIV 437
1 7 ZENKER F Diabetes insipidus und Trauma, W Nitsche Weissenfels 1919
1 7a PICKETS W Disturbances of metabolism with head injuries New Eng Jour Med 1947 CCXXXVI 858
1-8 KINDWALL J A and CLEVELAND D Pre frontal lobotomy fifteen patients before and after operation Am Jour Psychiat 1945 CI 749 ZIEGLER L H and OSGOOD C W A Edema and trophic disturbances of the lower extremities complicating pre frontal lobotomy Arch Neurol and Psychiat 1945 LIII 62
1-9 RISER LAZORTHE COUADAU and GERAUD Diabete insipide par polydipsie primaire au cours de l ablation d un kyste opto chiasmique recidevant Bull et Mem Soc med d Hop Paris 1945 LXI 414
130 KOURILISKY R DAVID M SICARD J and GALEY J J Diabete insipide posttraumatique—cessation subite de la soif au Vol IV 650

cours de l'ouverture d'un kyste arachnoidien de la region opto chiasmique guerison Rev Neurol 194 LXXIV 64
131 WARKANY J and MITCHELL A G Diabetes insipidus in children A critical review of etiology diagnosis and treatment with reports of four cases Am Jour Dis Child 1939 LVII 603
13 FINDLAYSON J Diabetes insipidus with great enlargement of the bladder Glasgow Med Jour 1881 XV 17
133 KOLZ in GERHARDT C Handbuch der Kinderkrankheiten VIII 1 H Laupp Tubingen 1887 1893
134 BLATT M L and GREENGARD J Diabetes insipidus Report of a case in a child Arch Pediat 19 6 XLIII 811
135 GAYLER Ueber das Zustandekommen der Wachstumsstorungen bei Diabetes insipidus des Kindes Monatschr f Kinderh 1921 XXI 156
136 TURNER H H Diabetes insipidus report of a case in a child Arch Pediat 19 8 LXV 433
137 DANERI J Diabetes insipidus Rev Chilena de Pediat 1934 V 06
138 WHITTLE Cited by EICHORN G Ueber Diabetes insipidus im Kindersalter Jahrb f Kinderh 1896 XLII 44
139 FLANDIN C POUMEAU DELILLE G PUECH and AUZEPY P Diabete insipide et obesite avec vergetures par atteinte infundibulo tuberienne d'origine ourlienne Bull et Mem Soc med d Hop de Paris 1935 LI 1 44
140 SALMI T Diabetes insipidus complicating chicken pox Duodecim 1936 LII 304
141 ROTHM H R Postvaccinal encephalitis associated with diabetes insipidus Am Jour Dis Child 193 XLIX 1 91
14 DAVIS J N P Diabetes insipidus and obesity in an Itesot leper child East African Medical Journal 1946 XXXIII 43
143 MUWAZI E M K and TROWELL H C Neurological disease among African natives of Uganda review of 69 cases East African Medical Journal 1944 XXI
144 GELFAND M The Sick African p 304 The Stewart Printing Co Capetown 1944
145 HEALY J W Diabetes insipidus as a manifestation of general miliary tuberculosis Brit Jour Child Dis 1935 XXXII 75
146 HAGENBACH E Ein Fall von Diabetes insipidus Jahrb f Kinderh 188 XIX 14
147 HAUSHALTER P and LUCIEN Polyurie simple et tubercle de l'hypophyse Rev neurol 1908 XII 1
148 HAND A Polyuria and tuberculosis Arch Pediat 1893 X 673 Defects of membranous bones exophthalmos and polyuria in childhood is it dyspituitarism Am Jour Med Sci 19 1 CLXII 509

149 SCHULLER A Ueber eigenartige Schadeldefekte im Jugendalter Fortschr a d Geb d Rontgenstrahlen 1915 16 XXIII 1
150 CHRISTIAN H A Defects in membranous bones exophthalmos and diabetes insipidus an unusual syndrome of dyspituitarism Med Clin N Am 1919 III 849 Defects in Membranous Bones Exophthalmos and Diabetes Insipidus contributions to medical and biological research vol 1 p 390 Paul B Hoeber New York 1919
151 HOCHSTETTER F Beitrag zur Klinik der Multiplen Blutdrusensklerose Med Klin 1922 XVIII 661
152 GRIFFITH J P C Xanthoma tuberosum with early jaundice and diabetes insipidus Arch Pediat 192 XXXIX, 297
153 ATKINSON F R B Schuller Christian s disease Brit Jour Child Dis 1937 XXXIV 8
154 SCHULTZ A WERMBTER F and PUHL H Eigentumliche granulomartige Systemerkrankung des hamatopoetischen Apparates Virchow s Arch f path Anat 19 4 CCLII 519
155 ROWLAND R S Christian s syndrome and lipoid cell hyperplasias of the reticulo endothelial system Ann Int Med 19 9 II 1 77 Pediatric investigation of essential xanthomatosis Schuller Christian type Trans Am Pediat Soc 193 XLIV 73
156 THANNHAUSER S J Serum lipoids and their value in diagnosis New England Jour Med 1947 CCXXXVII 546 Lipoidoses chapter VII-A Vol IV Oxford Medicine Oxford University Press 1949
157 PINKUS F and PICK L Zur Struktur und Genese der symptomatischen Zanthome Deutsch med Wochnschr 1908 XXXIV 14 6 PICK L and PINKUS F Über droppelbrechende Substanz in Hauttumoren ein Beitrag zur Kenntnis des Zanthome Monatsch f prakt Dermat 1908 V 545
158 CHESTER W Über Lipoidgranulomatose Virchow s Arch f path Anat 1930 CCLXXIX 561 FRASER J Skeletal lipoid granulomatosis (Hand Schuller-Christian s disease) Brit Jour Surg 1935 XXII 800 MORISON J M W Schuller s disease (reticulo endotheliosis) Brit Jour Radiol 1934 VII -13
159 SOSMAN M C Zanthomatosis Schuller-Christian s disease lipoid histiocytosis Jour Am Med Assoc 193 XCVIII 110
160 BLOTNER H Blood fat tolerance tests in malnutrition and obesity Arch Int Med 1935 LV 1-1
161 THOMA K H Eosinophilic granuloma with report of one case involving first the mandible later other bones and being accompanied by diabetes insipidus Am Jour Orthodontics (Oral Surgery Section) 1943 XXIX 641 JOHNSON C I and ZONDERMAN B Eosinophilic granuloma report of a case involving the frontal

bone Ann Otol Rhinol and Laryngol 1946 LV 938 GREEN W T and FARBER S Eosinophilic or solitary granuloma (relationship to Hand Schuller Christian s disease) Jour Bone and Joint Surg 194 XXIV 499 MALLORY T B Medical progress—pathology diseases of the bone New Eng Jour Med 194 CCXXVII 955 JAFFE H L and LICHTENSTEIN L Eosinophilic granuloma of bone Arch Path 1944 XXVII 99
162 MADDOX K Renal dwarfism Med Jour Australia 193 I 487 MITCHELL A G Nephrosclerosis (chronic interstitial nephritis) in childhood with special reference to renal rickets Am Jour Dis Child 1930 XL 101 145 345 388
163 CHARNOCK D A Renal rickets Jour Urol 1940 XLIV 850
164 GITTLEMAN I F and PINCUS J B Rickets associated with dwarfism glycosuria ketonuria and albuminuria Am Jour Dis Child 1940 LX 1351
165 BIEBER A Diabetes insipidus with pituitary dwarfism and grave renal calculosis case Rev Clin Pediat 1946 XLIV 27
166 BADER G B Renal rickets Jour Pediat 1934 IV 368
167 MOEHLIG R C Renal dwarfism or renal rickets Am Jour Roentgenol 1943 L 582
168 LEYDEN Ein Fall von Diabetes insipidus Berlin Klin Wochnschr 1865 II 373 OLLIVIER A De la polyurie et des variations de la quantite de l uree a la suite de l hemorrhagie cerebrale Arch de Physiologie normale et Pathologique Series 2 1876 III 85
169 LOWENBERG S A and SLOANE N G Diabetes of 20 years standing improved following subarachnoid hemorrhage Endocrinology 1940 XXVII 191
170 RASSULEV J A Ueber Diabetes insipidus bei Pellagra Arch f Schiffs u Tropen Hyg 1932 XXXVI 481
170a SPIES T D Personal communication
171 BELKOWSKI J Actinomycose de la base du crane et des meninges diabete insipide Rev de med Paris 1911 XXXI 415
172 STRAUCH A Hypophysial dystrophy in hydrocephalus Jour Am Med Assoc 1919 LXXII 1731
173 LENK R Akute Leukamie und Diabetes insipidus bei Status thymicolymphaticus Wien klin Wochnschr 1911 XXIV 1130
174 GRÜNTHAL E and KELLER F Diabetes insipidus mit Ausfall des hypothalamisch hypophysaren Systems Monatschr f Psychiat u Neurol 1943 CVIII 54
175 SHELDON J H Diabetes insipidus occurring in a case of lymphatic leukemia of the aleukaemic type Lancet 19 7 I 489
176 KUGELMEIER L M Plotzliches Auftreten eines Diabetes insipidus infolge septischer Nekrose in Hinterlappen und Stiel der Hypophyse

bei akuter myeloischer Stammzellenleukamie, Zeitsch f klin Med 1937 CXXXII, 521
177 LESNÉ E LAUNAY C and SÉE, G Diabete insipide au cours d une maladie de Besnier-Boeck Bull et Mem Soc med d Hop de Paris 1935, LI, 1137
178 TILLGREN, J Diabetes insipidus as symptom of Schaumann s disease benign lymphogranulomatosis Brit Jour Dermat 1935 XLVII 223
179 TENETA, S S Complications of brucellosis Klin Med, 1938 XVI 1 0
180 S VAISMAN B, S RAPAPORT T P SCHÜLLER H and H MONTES V Enfermedad reumatica y diabetes insipida Rev med de Chile, 1944 LXXII 419
181 GURVICH, M I and FARIGON N E Diabetes of malarial origin treated with quinine case, Soviet med 1940 IV 31
182 FLINKER R Ein Fall von Dystrophia musculorum progressiva mit Polyurie und Polydipsie, Deutsch Zeitschr f Nervenheill 1934 CXXXV 71
183 FUTCHER T B Diabetes insipidus with a report of five cases Johns Hopkins Hospital Reports 190 X 197
184 SOPHIAN, A Diabetes insipidus and osteitis fibrosa polycystica Jour Am Med Assoc 1930 VC 483
185 HEARD J D SCHUMACHER F L and GORDON W B Association of diabetes insipidus with osteitis fibrosa polycystica Am Jour Med Sci 1926 CLXXI 38
186 BACH M J and MIDDLETON, W S Multiple myeloma and diabetes insipidus Jour Am Med Assoc 1931 XCVII 306
187 MARIE J Le diabete insipide considere comme un trouble de le permeabilite des membranes cellulaires du nephron Hypopermeabilite a l eau et permeabilite conservee pour sodium chloride Bull et Mem Soc méd d Hop de Paris 194 LVIII 39
188 BLOTNER H The inheritance of diabetes insipidus Am Jour Med Sci 194. CCIV, 261
189 WEIL ADOLPH Über die hereditare Form des Diabetes insipidus Virchow s Arch f path Anat 1884 LXLV 70
190 WEIL ALFRED Uber die hereditare Form des Diabetes insipidus Deutsch Arch f klin Med 1908 LXLIII 180
191 LACOMBE L V De la polydipsia These de Paris No 99 1841
192 TROUSSEAU A Polydipsie clinique medicale de l Hotel-Dieu de Paris 1862 II 607
193 LANCERAUX E De la polyurie (diabete insipide) These de Paris 1869 WACHSMUTH Ein Fall von Diabetes insipidus Virchow s Arch f path Anat 1863 XXVI 318

194 CLAY R H Three cases of diabetes insipidus in one family Lancet 1889 I 1188
195 EHRMANN Familiarer Diabetes insipidus bei 5 geistig zuruck ge bliebenen Kindern, Berl klin Wochnschr 1911 XLVIII 496
196 DEBBREY Observation de polyurie Gaz d Hop 1859 546
197 REITH A Polydipsia treatment by large doses of valerian improve ment Med Times and Gaz 1866 I 309
198 ORSI F Curiosita cliniche sei individui d una stessa famiglia colpiti da idruria Gazz Med Ital 1881 XLI 35
199 MARINESCO G Deux cas de polyurie familiale dite essentielle Compt rend Soc de Biol S 10 1895 II 41
00 MARAÑON G *and* BONILLA E *A case of precocious and hered itary* diabetes insipidus Endocrinology 19 5 IX 46,
01 LANGE C DE Über erblichen Diabetes insipidus Jahrb f Kinder heilk (3 F) 1935 LXLV 1
0 PAIN G Notes a propos quelques observations de polyurie chro nique p 19 These de Paris No 427 1879
203 SASSE C Ein neuer Fall von hereditarem Diabetes insipidus Inaug Diss Bonn 1893
04 GEE S A contribution to the history of polydipsia St Barth Hosp Rep 1877 XIII 79
205 LAURITZEN M On hereditaer diabetes insipidus Hospitalstid 1893 (Ser 4) I 353 392 4 3 451
06 KNOPFELMACHER Diabetes insipidus bei Kindern Munch med Wochnschr 1905 I 6 9
207 McILRAITH C H Notes on some cases of diabetes insipidus with marked family and hereditary tendencies Lancet 189 II 767
208 CHASE L A Hereditary diabetes insipidus Canad Med Assoc Jour 19 7 XVII 12
209 CHESTER W and SPEIGEL L Hereditary diabetes insipidus *Jour Am Med Assoc 1933 C 806*
10 GÄNSSLEN and FRITZ Über Diabetes insipidus Klin Wochschr 19 4 III 22
11 LEVIT S G and PESSIKOVA L N The genetics of diabetes insipidus and its bearing on the problem of dominance in man Jour Hered 1936 XXVII 445
21 ELLERMAN M Hereditary diabetes insipidus Acta Psychiat et Neurol 1939 XIV 33
213 BULLOCH W The treasury of human inheritance Parts I and II Section 1a Diabetes insipidus Cambridge University Press Fetter Lane E C University of London 1909
214 JUST G Ein Wort zu Weils Diabetes insipidus Stammbaum Arch f Rassen u gesellsch Biol 19 4 5 XVI 31

215 HOGBEN L Genetic Principles in Medicine and Social Science p 44 Alfred A Knopf, New York 1932
16 ROGER H and ALLIEZ J Diabete insipide familial a propos de observations personalles Fol Neuropath Eston 1936 XV XVI 37
-17 MARTINEZ and NAVARRON Zwei Falle der familiaren Form des idiopatischen Diabetes insipidus mit Hypophysenbehandlung Rev d Circ med de Cobra 19 2 X 78
18 BONNET R Contribution a l etude du diabete insipide (publication d un cas de polyurie familial) Lyon 1936
219 FRANCESCHETTI A Heterochromia Bernard Horner syndrome dysraphia and familial diabetes with review of case Rev d Oto neuro ophth 1937 XV 42
2 0 KLAFTEN E Diabetes in ipidus und Schwangerschaft Monatschr f Geburtsh u Gynak 1926-27 LXXV 333
-21 FORSSMAN H On hereditary diabetes insipidus Acta Medica Scandanavica 1945 Supplement 150 p 1 to 196
2-2 HARDING F E The pituitary antidiuretic hormone in diabetes insipidus—8 cases of diabetes insipidus 4 with pregnancy West Jour Surg Obst and Gyn 1943 LI, -69
223 BLOTNER H Diabetes insipidus in one of twins New Eng Jour Med 1941 CCXXV 946
224 ROWNTREE L G Studies in diabetes insipidus Jour Am Med Assoc 19 4 LXXXIII 399
-5 RABINOWITCH I M Metabolic studies on a case of diabetes insipidus Arch Int Med 1921, XXVIII 355
-26 EICHORST H Practische Erfahrungen uber die zuckerige und einfache Harnruhr Cor-bl f schweiz Aerzte 1888 XVIII 393
2-7 GERHARDT D Der Diabetes insipidus Nothnagel s Specielle Pathologie und Therapie 1900 VII 7
28 FUTCHER T B A clinical report of nine cases of diabetes insipidus Trans Assoc Am Phys 1904 XIX 247
229 COHEN M MICHAEL and BLOTNER H Unpublished data
230 CHEYNE V D A description of the salivary glands of the rat and a procedure for their extirpation Jour Dent Research 1939 XVIII 457 TRIMBLE H C ETHERINGTON J and LOSCHE P K Rate of secretion of saliva and incidence of dental caries Jour Dent Research 1938 XVII -99 WEISBERGER D., NELSON C T and BOYLE P E The development of caries in the teeth of albino rats following extirpation of the salivary glands

Am Jour Orthodontics 1940 XXVI 88

231 STARLING Principles of Human Physiology p 874 edited and revised by C Lovatt Evans 8th Edition Lea and Febiger Philadelphia 1941
232 WEIR J F LARSON E E and ROWNTREE L G Studies in diabetes insipidus water balance and water intoxication study 1 Arch Int Med 19 XXIX 306
233 BLOTNER H Gastric analyses and gastric symptoms in diabetes insipidus Am Jour Digest Dis 1940 VII 73
234 BLOTNER H Effect of alcohol on digestion by gastric juice trypsin and pancreatin Jour Am Med Assoc 1936 CVI 1970
235 DODDS E C NOBLE R L SCARF R W and WILLIAMS P C Pituitary control of alimentary blood flow and secretions Changes produced in stomach by the administration of posterior pituitary extract Proceed Roy Soc London 1937 CXXIII 22 CUTTING W C DODDS E C NOBLE R L and WILLIAMS P C The effect of posterior pituitary extract on the alimentary secretions of intact animals Ibid 1937 CXXIII 27 Pituitary control of alimentary blood flow and secretion Gastric secretion and blood flow in hypophysectomized animals Ibid 1937 CXXIII 49
236 DE ANCIAES C J H Insuline pituitrine et secretion gastrique Compt rend Soc de Biol 19 6 LXLV ,13
237 KAULBERSZ J PATTERSON T L SANDWEISS D J and SALTZSTEIN H C Alterations in urogastrone excretion produced by extirpation of various endocrine glands Am Jour Physiol 1947 CL 373
238 MARAÑON G RICHET C PERGOLA A and LESUEUR G Acute abdominal syndromes of hypophyseal origin Lisboa Medica Lisbon 1939 XVI 589 abstract Jour Am Med Assoc 1940 CXIV 198
239 SNELL A M Water intoxication in diabetes insipidus Med Clin North America 19 8 9 XII 1667
240 ICHIJO T The effects of extract of pituitary gland on the sedimentation of red blood corpuscles of the normal and hypophysectomized dogs Sei I Kwai Med Jour 1934 LIII June abstract Sect p 5
240a KOURILSKY R and FOURNIER E Étude physiopathologique du diabete insipide humain Ann de Med 1948 IL 135
241 KEITH N M ROWNTREE L G and GERAGHTY J T A method for the determination of plasma and blood volume Arch Int Med 1915 XVI 547

-42 GIBSON, J G Jr and EVANS W A, Jr Clinical studies of the blood volume 1 Clinical application of a method employing the azo dye Evans blue and spectrophotometer Jour Clin Invest 1937 XVI 301
-43 FISCHER W J H Jr and BECK I Personal communication
44 TALBOTT T H COOMBS F S CANSOLAZIO W V and PECORA L J Diabetes insipidus associated with diabetes mellitus metabolic studies and report of a case, Arch Int Med 1940 LXVI 607
45 SOULE S D Diabetes insipidus and pregnancy Am Jour Obst and Gyn 1937 XXXIII 878
-45a CHIN H I LIU S H and YU T F Water and electrolyte metabolism in diabetes insipidus Proceed Soc Exper Biol and Med 1941 XLVI 682
246 FISCHER W J H, Jr and BOWMAN, R O The effect of intravenous solutions on the plasma volume hematocrit plasma protein and urinary output in the convalescent patient read before regional meeting of the American College of Physicians Hanover New Hampshire January -8 1947 unpublished to date
47 FOLIN O and WU H A system of blood analysis supplement 1 a simplified and improved method for determination of sugar Jour Biol and Chem 1920 XLI 367
-48 MOSENTHAL H O Interpretation of sugar tolerance tests Med Clin North America p 299 (March) 1947
-49 BLOTNER H Sugar tolerance tests methods and evaluation Am Jour Digest Dis 1947 XIV -45 Diagnosis of diabetes mellitus Proceed Am Diabetes Assoc 1947 VII 153
-50 GIBSON R B MAGERS E J and DULANEY H Blood sugar curves in diabetes insipidus and in habitual and experimental excessive water drinking Endocrinology 19 7 XI 341
251 JOHN H J Glucose tolerances and its value in diagnosis Jour Metab Res 192- L 497 1923 IV -55
252 LAWRENCE R D and HEWLETT R T L The effect of pituitrin and insulin on blood sugar Brit Med Jour 19 5 I 998
253 BLOTNER H and FITZ R The effect of insulin pituitrin and adrenalin on the blood sugar level Jour Clin Invest 19 7 V 51
254 BLOTNER, H Blood fat tolerance tests in malnutrition and obesity Arch Int Med 1935 LV 1-1
255 JOSLIN E P Fat and the diabetic New England Jour Med 1933 CCIX 519
-56 BLOOR W R The determination of small amounts of lipid in blood plasma Jour Biol Chem 1928 LXXVII, 53

257 RONY H R and LEVY A J Fat tolerance in obesity Jour Lab and Clin Med 1929 XV 1
58 CHAIKOFF I L McGAVACK T H and KAPLAN A The blood lipids in the post absorptive state and after the ingestion of fat in normal human subjects and in a case of disseminated cutaneous xanthomata Jour Clin Invest 1934 XIII 1
59 ANSELMINO K J and HOFFMAN, F Das Fettstoffwechsel hormon der Hypophysenvorderlappens Klin Wochnschr., 1931 X 380
260 GOLZIEHER M A SHERMAN I and ALPERSTEIN B B The fat tolerance test in pituitary disease Endocrinology 1934 XVIII 505
261 MUÑOZ J M Action de l extract antero hypophysaire sur les lipids du sang Compt rend Soc de Biol 1933 CXII 50
262 EVANS E I Diabetogenic principle of the anterior pituitary Proceed Soc Exper Biol and Med 1933 XXX 1370
63 COOPE, R and CHAMBERLAIN E N The effect of pituitrin on the fatty acid of the liver Jour Physiol 1925 LX 69
64 NEUBAUER C and VOGEL J Anleitung zur qualitativen und quantitativen Analyse des Harns p 353 Kreidel Wiesbaden 1872
65 OPPENHEIM H Casuisticher Beitrag zur Polyurie Zeitschr f klin Med 188 V 618 Weiterer Beitrag zur Polyurie Zeitschr f klin Med 1883 VI 556
266 FITZ R A case of diabetes insipidus Arch Int Med 1914 XIV 706
267 ROSENBLOOM J and PRICE, H T A metabolism study of a case of diabetes insipidus Am Jour Dis Child 1916 XII 53
68 CURTIS G M The production of experimental diabetes insipidus Arch Int Med 19 4 XXXIV 801
269 SWAN H G Sodium chloride and diabetes insipidus Am Jour Physiol 1939 CXXVI 341
270 PETERS J P Body Water p 323 Charles C. Thomas Springfield Illinois 1935
271 VEIL W H Über intermediare Vorgange beim Diabetes insipidus und ihre Bedeutung fur die Kenntnis von Wesen dieses Leidens Biochem Zeitschr 1918 XCI 317
72 BUTLER A M HARPER E A and CAREY B W Jr Excretion of sodium and chloride in normal persons and in patients with nephritis and diabetes insipidus Am Jour Dis Child 1933 XLVI 1459
273 WILLIAMS J R Diabetes insipidus A metabolic study of the effect of pituitary administration Endocrinology 1917 I 312

242 GIBSON, J G JR and EVANS W A JR Clinical studies of the blood volume 1 Clinical application of a method employing the azo dye Evans blue and spectrophotometer, Jour Clin Invest 1937 XVI 301
243 FISCHER W J H JR and BECK I Personal communication
244 TALBOTT T H COOMBS F S CANSOLAZIO W V and PECORA L J Diabetes insipidus associated with diabetes mellitus metabolic studies and report of a case Arch Int Med 1940 LXVI 607
245 SOULE S D Diabetes insipidus and pregnancy Am Jour Obst and Gyn 1937, XXXIII 878
245a CHIN H I LIU, S H and YU T F Water and electrolyte metabolism in diabetes insipidus Proceed Soc Exper Biol and Med 1941 XLVI 682
246 FISCHER W J H JR and BOWMAN R O The effect of intravenous solutions on the plasma volume hematocrit plasma protein and urinary output in the convalescent patient read before regional meeting of the American College of Physicians Hanover New Hampshire January 28 1947 unpublished to date
247 FOLIN O and WU H A system of blood analysis supplement 1 a simplified and improved method for determination of sugar Jour Biol and Chem 1920 XLI 367
248 MOSENTHAL H O Interpretation of sugar tolerance tests Med Clin North America p 99 (March) 1947
249 BLOTNER H Sugar tolerance tests methods and evaluation Am Jour Digest Dis, 1947 XIV 245 Diagnosis of diabetes mellitus Proceed Am Diabetes Assoc 1947 VII 153
250 GIBSON R B MAGERS E J and DULANEY H Blood sugar curves in diabetes insipidus and in habitual and experimental excessive water drinking Endocrinology 1927 XI 341
251 JOHN H J Glucose tolerances and its value in diagnosis Jour Metab Res 1922 L 497 1923 IV 255
252 LAWRENCE R D and HEWLETT R F L The effect of pituitrin and insulin on blood sugar Brit Med Jour 1925 I 998
253 BLOTNER H and FITZ R The effect of insulin pituitrin and adrenalin on the blood sugar level Jour Clin Invest 1927 V 51
254 BLOTNER H Blood fat tolerance tests in malnutrition and obesity Arch Int Med 1935 LV 121
255 JOSLIN E P Fat and the diabetic New England Jour Med., 1933 CCIX 519
256 BLOOR W R The determination of small amounts of lipid in blood plasma Jour Biol Chem 1928, LXXVII 53

90 MAURER F E Ueber den Jodgehalt des Blutes und seine Veranderungen in Menstruation und Graviditat Arch f Gynak 1927 CXXX 70

91 NITZECU I I and BINDER E Iodemie normale variations saisonniers iodemie des goitreux Compt rend Soc de Biol 1931 CVIII 79

92 DAVIS C B CURTIS G M and COLE, V V Blood iodine studies II The normal iodine content of human blood Jour Lab & Clin Med 1934 XIX 818

93 McCULLAGH D R Studies in blood iodine by the use of a new chemical method Cleveland Clinic Quarterly 1935 II 15

94 PERKIN H J and CATTELL, R B The practicability and significance of blood iodine estimations New York State Jour Med 1936 XXXVI 1033

95 UNPUBLISHED DATA

96 CURTIS G M and PUPPEL I D Increased urinary excretion of iodine in hyperthyroidism Arch Int Med 1937 LX 498

97 PERKIN H J and HURXTHAL L M The fractionation of the iodine of the blood in thyroid disease Jour Clin Invest 1939 XVIII 733

298 PERKIN H J BROWN B B and LANG J Blood iodine content of normal and thyrotoxic individuals iodine tolerance test Canad Med Assoc Jour 1934 XXXI 365 PERKIN H J and LAHEY F H The iodine tolerance test as an aid in the diagnosis of clinical hyperthyroidism New Eng Jour Med 1937 CCXVI 501

299 FITZ R and HUNT R S Experiences with an iodine tolerance test in hypothyroid patients Trans Assoc Am Physicians 1937 LII 4

300 WINER N J and BLOTNER H Renal function in diabetes insipidus Arch Int Med 1942 LXX 61

301 BLOTNER, H Alcohol tolerance tests in normal individuals and in patients with diabetes mellitus and diabetes insipidus New Eng Jour Med 1939 CCXX 83

302 GIBSON J G 2ND and BLOTNER H The determination of ethyl alcohol in blood and urine with the photoelectric colorimeter Jour Biol Chem 1938 CXXVI 551

303 AMBARD L Physiologie Normale et Pathologique des Reins p 15 Second edition Masson & Cie Paris 1920

304 WIDMARK E M P Über die Konzentration des genossenen Alkohols in Blut und Harn unter verschiedenen Umstanden Skandinav Arch f Physiol 1916 XXXIII 85

305 HAGGARD H W and GREENBERG L A Studies in absorption distribution and elimination of ethyl alcohol the excretion

274 BLUMGART H L Diabetes insipidus with particular reference to further experience with treatment by pituitary extract applied intranasally, Med Clin North America 1932, XV, 895
275 WEIR J F Pituitary extract on metabolism of diabetes insipidus Arch Int Med 1923 XXXII 617
276 WHITE H L and FINDLEY, T JR Responses of normal subjects and of patients with diabetes insipidus to water and salt ingestion Jour Clin Invest 1939 XVIII 377
277 WINTER C A, INGRAM W R and GROSS E G Effect of pitressin injections upon the serum electrolytes and water exchange of cats with diabetes insipidus and adrenal insufficiency Am Jour Physiol 1939 CXXVI 656
278 SMITH F M and MACKAY E M Influence of posterior pituitary extract on sodium balance in normal subjects and in patients with diabetes insipidus Proceed Soc Exp Biol and Med, 1936, XXXIV 116
279 MAINZER F Uber Fragen der Hypophysenhinterlappentherapie des Diabetes insipidus Wien Arch Inn Med 1935 XXVI 101
280 BLOTNER, H Blood and urine chlorides in 22 cases with diabetes insipidus Am Jour Med Sci 1941 CCII, 222
281 BLOTNER H The calcium and phosphorus in the cerebrospinal fluid in diabetes insipidus Am Jour Med Sci 1940 CC 39
282 MANCHESTER R C Influence of posterior pituitary extracts on mineral and water exchange in children, Proceed Soc Biol and Med 1931-32 XXIX 717
283 FULTON M N VAN AUKEN H A PARSONS R J and DAVENPORT L F Comparative effect of various diuretics in dogs with special reference to excretion of urine chloride and urea Jour Pharm and Exp Ther 1934 L 23
284 LINDEBOOM G A Beobachtungen bei einem Fall von Diabetes insipidus et mellitus Deutsch Arch f klin Med 1933 LXXIV 175
285 BLOTNER H The amount of iodine in the blood and urine in patients with diabetes insipidus Am Jour of Med Sci 1942 CCIII 708
286 PERKIN H J and LAHEY F H The level of iodine in the blood Arch Int Med 1940 LXV 882
287 PERKIN H J Determination of iodine in the blood Biochem Jour 1933 XXVII, 1078
288 CURTIS G M and PUPPEL I D The normal urinary iodine in man J Lab and Clin Med 1937 XXII 1014
289 SCHERINGER W Beitrag zur Kenntnis des Blutjodspiegels beim Weibe unter physiologischen Bedingungen Arch f Gynak 1930 CXLIII 319

321 BLOTNER H and KUNKEL P Diabetes insipidus and pregnancy New England Jour Med 194 CCXXXII 87
322 FRENCH H The influence of pregnancy upon certain medical diseases and of certain medical diseases upon pregnancy Brit Med Jour 1908 I 1165 1172
323 BOISSARD Discussion of Chavane and Faure Miller (337)
324 BAR Discussion of Chavane and Faure Miller (337)
325 KOLLE Demonstration Gravidtat bei Diabetes insipidus Zentralbl f Gynak 1926 L 1
326 ARTAUD A Un cas de grossese au cours d un diabete insipide Bull Soc d Obst et de Gynec 1933 XXII 196 198
327 SOULE S D Diabetes insipidus and pregnancy Am Jour Obst and Gynec 1937 XXXIII 878 890
328 VERDEUIL and CASALTA Une observation de diabete insipide et gravidite Bull Soc d Obst et de Gynec 1938 XXVII 87
329 MOMIGLIANO E Diabete insipido e gravidanza Ann di Ostet e Ginec 19 9 LI 905-979
330 DUNCAN J M On diabetes insipidus in pregnancy and labour Trans Obst Soc London 1888 XXIX 308 316
331 VINAY C Diabete insipide et grossesse Semaine med 1899 XIX 14
332 MERBACH Cited by Muller P Die Krankheiten des weiblichen Korpers in ihren Wechselbeziehungen zu den Geschlechtsfunctionen p 508 Stuttgart 1888
333 KATZ H Cited by HEIDLER H (348) Zentralbl f Gynal 1924 XLVIII 357-363
334 DUVOIR M POLLET L and CACHIN M Diabete insipide suivi de diabete sucre avec coma influence de grossesses sur la polyurie traitment par la folliculine Bull et Mem Soc med d Hop de Pari 193 XLVIII 549 551
335 CARTER P J Diabetes insipidus in pregnancy case report Urol and Cutan Rev 1940 XLIV 549 551
336 THOMSON K J HIRSHEIMER A GIBSON J G Jr and EVANS W A Jr Studies on circulation in pregnancy III Blood volume changes in normal pregnant women Am Jour Obst and Gyn 1938 XXXVI 48 59
337 CHAVANE and FAURE MILLER R Diabete insipide et grossesse Bull Soc d Obst et de Gynec 1900 III 400 409
338 KLAFTEN E Diabetes insipidus and Schwangerschaft Monatschr f Geburtsh u Gynak 19 7 LXXV 333 349
339 BALLERINI Per la genesi del diabete insipido e delle poliurie gravidiche Folia Gynaec 19 1 XIV 97

of alcohol in urine and expired air the distribution of alcohol between air and water blood and urine Jour Pharmacol and Exper Therap 19,4 LII 150
306 NEWMARK L A case of infundibular tumor in a child causing diabetes insipidus with tolerance of alcohol, Arch Int Med, 191, XIX 550
307 MILES W R The comparative concentrations of alcohol in human blood and urine at intervals after ingestion, Jour Pharmacol and Exper Therap 19 - XX 26,
308 WIDMARK E M P Hormonale Einflusse auf den Alkoholumsatz Biochem Zeitschr, 1935 CCLXXVII 79
309 BLOTNER H The calcium and phosphorus in the cerebrospinal fluid in diabetes insipidus Am Jour Med Sci, 1940 CC -35
310 CLARK E P and COLLIP J B Tisdall method for determination of blood serum calcium with a suggested modification Jour Biol Chem 19-5, LXIII 461
311 FISKE, C H and SUBBAROW, Y Colorimetric determination of phosphorus Jour Biol Chem 19-5 LXVI 375
31 MERRITT, H H and FREMONT-SMITH F The Cerebrospinal Fluid p 27 W B Saunders Co, Philadelphia 1938
313 McLEAN F C and HASTINGS A B The state of calcium in the fluids of the body Jour Biol Chem 1935 CVIII 85
314 CANTAROW, A The calcium content of cerebrospinal fluid Arch Int Med 19 9 XLIV 667 The relationship between the calcium content of cerebrospinal fluid and blood serum Arch Int Med, 19 9 XLIV 670
315 MERRITT H H and BAUER W The calcium content of serum cerebrospinal fluid and aqueous humor at different levels of para thyroid activity Jour Biol Chem 1931 XC 215
316 COHN D J KAPLAN I and LEVINSON, A A study of cal cium and phosphorus in cerebrospinal fluid Jour Lab and Clin Med 1939 XXIV 609
317 GREGORY R and ANDERSCH M The filterable calcium of blood serum a comparison of filterable calcium of serum and total calcium of cerebrospinal fluid in normal hyperparathyroid and hypoparathyroid states Am Jour Med Sci 1936 CXCI 263
318 McLEAN F C and HASTINGS A B Clinical estimation and sig nificance of calcium ion concentration in the blood Am Jour Med Sci 1935 CLXXXIX 601
319 BRYAN A H and METZGER M A The insensible loss of water in diabetes insipidus Am Jour Med Sci 1938 CXCVI 3
320 S A ROBINS Professor of Roentgenology at Tufts College Medical School made the intravenous urograms

359 NOVAK J Diabetes insipidus in graviditate Berl klin Wochnschr 1917 LIV 107 109
360 VICKERS D M Diabetes insipidus with acute retention in pregnancy report of a case Surg Gynes and Obst 1924 XXXVIII 3 5
361 LAURENTIE A and BASILIOU B J Crisis eclamptiques sans albuminurie avant apparu le e jour des suites de couches amaurose et diabete insipide contribution a l etude pathogenique du diabete insipide dans ses rapports avec l eclampsie Gynec et Obst 19 6 XIII 3 1 331
362 JANSEN R Über Diabetes Insipidus (ein Besonderer Fall) Inaugural Dissertation Halle C A Kaemmerer & Co 1899
363 TELLETAAR J Diabetes insipidus and pregnancy Orvosi hetil 19 9 LXXIII 701
364 MARAÑON G Un caso de diabetes insipida gravidica con poliuria enorme y probable lesion tuberculosa de lobula posterior de hipofisis Arch Med Madr 1926 XXII 289
365 PRIBRSKY J Diabetes insipidus and pregnancy Časop lek cesk 1934 LXXIII 60 299 and 3
366 SCHELLENBERG P Diabetes insipidus und Graviditat ein Beitrag zur Aetiologie des Diabetes insipidus p 61 Inaugural Dissertation Konigsberg Johan Raabe 1930
367 LAUTER S and HILLER F Diabetes mellitus and Diabetes insipidus in Auschluss an Schwangerschaft Deutsches Arch f klin Med 1925 CXLVI 355 361
368 SKROBSNSKI K K Über das Verhaltnis des Diabetes mellitus und insipidus zu den weiblichen Geschlechtsorgane und Schwangerschafte Zentralbl f Gynak 190 XXVI 1038
369 KLEINWACHTER L Der Diabetes von gynakologischen Standpunkt aus betrachtet Zeitschr f Geburtsh u Gynak 1898 XXXVIII 191 233
370 HENRIET P Glycosuries et diabetes en pratique obstetricale Rev franç de Gynec et d Obst 1936 XXXI 111 128
371 SILVA G Diabetes insipidus und Schwangerschaft Bol an clin Obst Santiago del Chile 1927 XIV 77
372 DELLEPIANE G Sul diabete insipido complicante la gravidanza Boll d Soc Piemontese di Ostet de Ginec 1934 II 4 9 450
373 SPAIN A W and GEOGHEGAN F Diabetes insipidus in association with postpartum pituitary necrosis Jour Obstet and Gynec Brit Emp 1946 LIII 2 3
374 SHEEHAN H L and MURDOCH R Postpartum necrosis of anterior pituitary pathological and clinical aspects Jour Obstet and Gynecol Brit Emp 1938 XLV 456

340 BENNETT J H Clinical Lectures on the Principles and Practice of Medicine p 1037, Fifth Edition Edinburgh 1868
341 DUNCAN J M On diabetes insipidus in pregnancy and labour Trans Obst Soc London 1888, XXIX 308-316
34 SHAMBERG, J F A case of exaggerated polyuria of pregnancy Univ Mag 1893-94 VI 385
343 VOITURIEZ J De la polyurie gravidique, J de Soc med de Lilles 1890 I 457-467
344 ESTERLE Cited by TARNIER S and BUDIN, P Traite de l art des Accouchements, vol II p 586 G Steinheil Libraire Editeur Paris, 1886
345 VINAY C Diabete insipide et grossesse Semaine med 1899 XIX 14
346 NOVAK J Diabetes insipidus in graviditate Berl klin Wochnschr 1917 LIV 107-109
347 LICHWITZ L Drei Falle von Simmondscher Krankheit Klin Wochnschr 1922 I 1877-1879
348 HEIDLER H Kongenitale Hautdefekte bei Neugeborenen Zentralbl f Gynak 1924 XLVIII 357-363
349 FRÜHINSHOLZ A VERMELIN H and HENNEQUIN Diabete d origine hypophysaire et gestation Bull Soc d Obst et Gynec 1928 XVII 741-744
350 EDELMANN J G and KRITZMAN, A S Ein Fall von Diabetes insipidus bei einer Schwangeren mit Lues ignorata Bericht u d ges Gynak u Geburtsh 1926 X 325
351 MESTITZ W Ein Fall von transitorischer Polyurie und Polydipsie am normalen Schwangerschaftsende Zeitschr f Geburtsh u Gynak 1930 LXLVIII 1-3-1-9
352 ANSELMINO K J and HOFFMAN F Diabetes insipidus und Schwangerschaft Zentralbl f Gynak 1930 LIV -061- 068
353 DIETEL H Diabetes insipidus und Schwangerschaft Arch f Gynak 1935 CLIX 404 409
354 BRATTSTROM E Ein Fall von Diabetes insipidus traumaticus und Graviditat Acta Obst et Gynec Scandinav 1938 XVIII 320-3 4
355 BLEAKLY J Case of diabetes insipidus and twin pregnancy Proceed Roy Soc Med 1938 XXXI, 1062-1064
356 MERLINO A Diabete insipido complicante la gravidanza Arch di Ostet e Ginec 1938 II 1-1-143
357 HART S D and BREITMAN H B Diabetes insipidus complicating pregnancy Am Jour Obst and Gynec 1941 XLI 527
358 EDELMANN J G and KRITZMAN A S Ein Fall von Diabetes insipidus bei einer Schwangeren mit Lues ignorata Bericht u d ges Gynak u Geburtsh 19 6 X 325

389 JOSLIN E. P., ROOT H F WHITE, P MARBLE A and BAILEY C C The treatment of diabetes mellitus Lea and Febiger Philadelphia 1946 p 7 5
390 STEINER F Zur Erblichkeit des Diabetes insipidus Der Erbarzt 1939 VII 89
391 HOUSSAY B A Carbohydrate metabolism New England Jour Med 1936 CCXIV 971
39 LONG C N H The influence of the pituitary and the adrenal glands upon pancreatic diabetes Medicine 1937 XVI 15
393 YOUNG F G Experimental investigations on relationship of anterior hypophysis to diabetes mellitus Proc Roy Soc Med 1938 XXXI 1305
394 HAM A W and HAIST R E Histological study of trophic effects of diabetogenic anterior pituitary extracts and their relation to the pathogenesis of diabetes Am Jour Path 1941 XVII 787
395 RICHTER C P Experimental diabetes insipidus its relationship to the anterior and posterior lobes of the hypophysis Am Jour Physiol 1934 CX 439
396 MOMPO ALIÑO L Association of diabetes mellitus and diabetes insipidus in hypophyseal infantalism heterologous transplantation of pituitary body Rev Clin españ 1941 II 31
397 LINDEBOOM G A Beobachtungen bei einem Fall von Diabetes insipidus et mellitus Deutsches Arch Fur Klin Med 1933 CLXXV 74
398 MOLONEY G E Diabetes mellitus associated with diabetes in sipidus New Zealand Med Jour 1939 XXXVIII 63
399 RUTLEDGE D I and RYNLARSON E H Diabetes insipidus Treatment by insufflation of powdered substances Proc Staff Meet Mayo Clinic 1939 XIV 443
400 SCHUNTERMANN C F Fall von Diabetes insipidus mit Diabetes mellitus Klin Wochnschr 1930 IX
401 HEIBERG K A Ein Fall von gleichzeitigem Diabetes insipidus und diabetes mellitus Ztschr f Klin Med 1911 LXXIII 319
402 FREUND H Untersuchungen uber einem Fall von Gleichzeitig bestehenden Diabetes mellitus and insipidus Klin Wochnschr 19 I 1780
403 CIPRIANI C R MORACCHINI R and ROLTTA C Diabetes insipido e diabetes mellito in acromegalica con struma adenoma del l ipofise e sclerosis del pancreas Arch per le Sc med 19 9 LIII 337
404 di GUGLIELMO G Diabete mellito e lesioni ipofisarie Boll d Soc med chir di Pavia 19 7 II 319

375 TROISIER J Action antipolyuriques des hautes doses de folliculine dans le diabete insipide de l homme Bull et Mem Soc med d Hop de Paris 193 XLVIII 1451
376 BELTRAMETTI L Die Sexual funktionen in ihren Beziehungen zum Wasserhaushalt insebesondere zum Diabetes insipidus Endokrinologie, 1935, XVI, 241
377 BLOTNER H Effect of amniotin and antuitrin S in diabetes insipidus New England Jour Med 1937, CCXVII 59
378 HARDING, F E The pituitary antidiuretic hormone in diabetes insipidus Eight cases of diabetes insipidus—four with pregnancy West Jour Surg, Obst and Gyn 1943 LI 269
378a DANDY W E Section of the human hypophysial stalk Its relation to diabetes insipidus and hypophyseal function, Jour Am Med Assoc 1940 CXIV 312
379 FISHER C MAGOUN, H W and RANSON S W Dystocia in diabetes insipidus the relation of pituitary oxytocin to parturition Am Jour Obst and Gyn, 1938, XXXVI 1
380 SENATOR H Ueber die Beziehungen zwischen Diabetes mellitus und insipidus Deutsches med Wochnschr, 1897, XXIII 385
381 GREENE J A and GIBSON, R B Coexistance of diabetes mellitus and diabetes insipidus Jour Lab and Clin Med 1938-39 XXIV 455
382 ALLAN, F N and ROWNTREE, L G The association of diabetes insipidus and diabetes mellitus, Endocrinology, 1931, XV 97
38 a BANERJEE S A case of diabetes insipidus associated with diabetes mellitus Indian Med Gaz, 1947, LXXXII 478
383 LAWRENCE R D and McCANCE R A Diabetes mellitus and diabetes insipidus associated in one case Lancet 1933 I 76
384 McPHERSON E Case of diabetes mellitus associated with lesions of the pituitary body Glasgow Med Jour 1939 CXXXI 2 0
385 TALBOTT J H COOMBS F S CONSOLAZIO W V and PECORA L J Diabetes insipidus associated with diabetes mellitus metabolic studies and report of a case, Arch Int Med 1940 LXVI 607
386 LEWIN C Zur Frage des Zusammenhangs des Diabetes mellitus und Diabetes insipidus Med Klin 1919 XV, 133
387 TESCHEMACHER Ueber die Fortdauer der Polyurie bei Diabetikern nach vollstandig verschwundener Glykosurie und der Uebergang von Diabetes mellitus in Diabetes insipidus Munchen Med Wochnschr 1907 I 561
388 D AMATO L Due casi di diabete insipido trasformati in diabete mellito Riforma med 190 II, 411

pituitary extract and the influence of ephedrine thereupon Jour Pharmacol and Exper Therap 1938 LXIV 86
419 STARR I GAMBLE C J MARGOLIES A DONAL J S Jr JOSEPH N and EAGLE E A clinical study of the action of 10 commonly used drugs on cardiac output work and size on respiration on metabolic rate and on electrocardiograms Jour Clin Invest 1937 XVI 799
420 LOWELL F C Immunologic studies in insulin resistance I Report of a case exhibiting variations in resistance and allergy to insulin Jour Clin Invest 1944 XXIII 225 Immunologic studies in insulin resistance II The presence of a neutralized factor in the blood exhibiting some characteristics of an antibody Jour Clin Invest p 233 Immunologic studies in insulin resistance III Measurement of an insulin antagonist in the serum of an insulin resistant patient by the blood sugar curve method in mice Jour Clin Invest 1947 XXVI 57
420a WILLIAMS R H and COLE E H Nephrogenic diabetes insipidus transmitted by females and appearing during infancy in males Ann Int Med 1947 XXVII 84
421 GREENE J A and JANUARY L E Diabetes insipidus treated by the subcutaneous administration of a suspension of pitressin tannate in oil Jour Am Med Assoc 1940 CXV 1183 Efficacy of pellets of posterior hypophysis and of pitressin in oil in diabetes insipidus Proceed Soc Exper Biol & Med 1940 XLIV 17
422 STEPHENS D J Pitressin in oil prolonged antidiuretic effect in experimental and clinical diabetes insipidus Jour Clin Invest 1941 XX 463
423 THORN G W and STEIN K E Diabetes insipidus and pitressin pitressin tannate therapy in diabetes insipidus Jour Clin Endocrinology 1941 I 680
424 BLOTNER H Pitressin tannate in oil in the treatment of diabetes insipidus Jour Am Med Assoc 1942 CXIX 995
425 LACY C S Three cases of diabetes insipidus successfully treated by ergot Med News 1883 XLII 9
426 EICHORST H Praktische Erfahrungen uber die zuckerige und einfache Harnruhr Cor Bl f Schweiz Aertze 1888 XVIII 393 SCHERF D Pyramidon beim Diabetes insipidus Wien Arch f inn Med 1932 XXII 457 DeGOWIN E L Diabetes insipidus Am Jour Med Sci 1935 CXC 747
427 KAHN B S Use of amidopyrine in a case of diabetes insipidus Jour Am Med Assoc 1933 C 1593
428 GRANT F C Surgical experience with tumors of the pituitary gland Jour Am Med Assoc 1948 CXXXVI 668

405 GRAY P A and MOFFAT, W M Coexistance of diabetes mellitus and diabetes insipidus Case report with autopsy, Endocrinology, 1940 XXVII 430
406 FRADISS L Le diabete insipide Ollier-Henry Éditeur These Paris 1926 BIGGART J H Anatomical basis for resistance to pituitrin in diabetes insipidus Jour Path and Bact 1937 XLIV 305
407 LEARY T Excess cholesterol as a pathogenic agent p 3 Proceed 50th Anniversary, Tufts College Medical School Tufts Medical Alumni Association Boston 1944 The genesis of atherosclerosis Arch Path 1941 XXXII 507
408 BROWN W E Jr and RYNEARSON, E H A procedure for the diagnosis of diabetes insipidus Proceed Staff Meeting Mayo Clinic, 1944 XIX 67
409 ABEL J J ROUILLIER C A and GEILING E M K Further investigations on the oxytocic-pressor diuretic principle of the infundibular portion of the pituitary gland Jour Pharmacol and Exper Therap 19-3 XXII -89
410 KAMM O ALDRICH T B GROTE, I W ROWE, L W and BUGBEE E P The active principles of the posterior lobe of the pituitary gland I The demonstration of the presence of the active principles II The separation of the two principles and their concentration in the form of potent solid preparations Jour Am Chem Soc 19 8 L 573
411 STEHLE R L New method for separating pressor and oxytocic substances from posterior lobe of pituitary gland Jour Biol Chem 1933 CII 573
41 PHARMACOPOEIA of the U S A (the U S P) U S P XIII Edition April 1947 p 414
413 SMITH F M Diabetes insipidus treatment by intranasal insufflation of posterior pituitary powder Jour Am Med Assoc 1934 CII 660
414 CHOAY A and CHOAY L Vingt ans de traitement du diabète insipide par prises nasales de poudre de lobe posterieur d hypophyse Presse med Paris 1946 LIV 500
415 REES M H and OLMSTED W H The use of pituitary extracts by mouth in the treatment of diabetes insipidus Endocrinology, 192 VI 230
416 GEILING E M K and OLDHAM F K The neurohypophysis Jour Am Med Assoc 1941 CXVI 30
417 MOFFAT W M The effect of pituitrin injections on blood pressure in man Am Jour Med Sci 1933 CLXXXVI 854
418 STEHLE, R L See reference 411 MILLVILLE K I Electrocardiographic and blood pressure changes induced by posterior

443 McPHEDRAN H Three cases of diabetes insipidus one associated with toxic goiter Canad Med Assoc Jour., 1938 XXXIX 370 The thyroidectomy was partial personal communication to the author
444 FERRO LUZZI G La tiroidectomia nel diabete insipido Minerva Med 1937 II 557
445 FINDLEY T Jr Thyroid pituitary relationship in diabetes insipidus Ann Int Med 1937 XI 701
446 ASTWOOD E B Treatment of hyperthyroidism with thiourea and thiouracil Jour Am Med Assoc 1943 CXXII 78 ASTWOOD E B and VANDERLAAN W P Propylthiouracil Jour Clin Endocrinol 1945 V 4 4
447 REVENO W S Effect of thiouracil on human tissues Jour Clin Endocrinol 1945 V 403
448 MEYER NOBLE K Beeinflussung eines Falles von Diabetes insipidus durch Corpus luteum Extrakt Munch med Wochnschr 1930 LXXVII 1844
449 TEEL H M Diuresis in dogs from neutralized alkaline extracts of the anterior hypophysis Jour Am Med Assoc 19 9 XCIII 760 TEEL H M and CUSHING H Studies in the physiological properties of the growth promoting extracts of the anterior hypophysis Endocrinology 1930 XIV 157
450 BIASOTTI A Thyroide et action diuretique de l extrait antehypophysaire Compt rend Soc de Biol 1934 CXV 3 9
4 1 TROISIER J Action antipolyurique des hautes doses de folliculine dans le diabete insipide de l homme Bull et Mem Soc med d Hop de Paris 1932 XLVIII 1451
45 PEITRAMETTI L Die sexualfunktionen in ihren Beziehungen zum Wasserhaushalt insbesondere zum Diabetes insipidus Endokrinologie 1935 XVI 241
453 ASTWOOD E B Personal communication
453a SHAPIRO B G Control of urinary secretion by the anterior pituitary Lancet 1938 II 1457
454 BLOTNER H Effect of amniotin and antuitrin in diabetes insipidus New England Jour Med 1937 CCXVII 59
455 BARNES B O., REGAN J F and NELSON W O Improvement in experimental diabetes following the administration of amniotin Jour Am Med Assoc 1933 CI 9 6
456 COLLENS W S SLOBODKIN S G ROSENBLIETT S and BOAS L C The effect of estrogenic substance on human diabetes Jour Am Med Assoc 1936 CVI 678
457 SILVESTRI T Diabete insipido e puberta Riforma med., 19 1 XXXVII 412

4 8a WEINSTEIN E A and SPINGARN C L Diabetes insipidus Jour Mt Sinai Hospital 1940 VII 90

4-9 ROWLAND R S Xanthomatosis and the reticulo endothelial system correlation of unidentified group of cases described as defects in membranous bones exophthalamos and diabetes insipidus (Christian s syndrome) Arch Int Med 1928 XLII, 611

430 SCHÜLLER A and CHIARI H Ein Fall von Xanthomatose Wien klin Wochnschr 1930 XLIII 153

431 HOFER K Beitrag zur Xanthomatose der Dura Mater und der Schadelknochen Klin Wochnschr 1930 IX 130

43 LEVINSON A Diabetes insipidus Am Jour Dis Child 19 6 XXXII 154 MEIJERS E J Diabetes insipidus in children Nederl tijdschr v geneesk, 19 9 II 5336 ROWNTREE L G Diabetes insipidus Jour Am Med Assoc 1924 LXXXIII 399

433 EBSTEIN W Beitrage zur Lehre von Diabetes insipidus Deutsch Arch f klin Med 1909 XCV 1

434 BENARIO J Zur Pathologie und Therapie des Diabetes insipidus Munch med Wochnschr 1913 LX 1768

435 UMBER Berlin gesellschaft fur Chirurgie Deutsch med Wochnschr 192 XLVIII 1 21

436 CHRISTIE C D and STEWART G N Study of some cases of diabetes insipidus with special reference to the detection of changes in the blood when water is taken or withheld Arch Int Med 19 2 XXIX 555

437 HERRICK J B Report of a case of diabetes insipidus with marked reduction in the amount of urine following lumbar puncture Arch Int Med 1912 X 1

438 CAMMIDGE P J Complete recovery from diabetes insipidus Practitioner 19 0 CV -44

439 ALLEN F M and SHERRILL J W Diet treatment of diabetes insipidus Jour Metab Research 1923 III 479

440 HIRSCH O and DEMEL R Ueber Implantation von tierscher und menschlicher Hypophyse bei Diabetes insipidus Wien klin Wochnschr 1936 XLIX 523

441 HIRSCH O Rolle der Hypophyse und des Hypothalamus beim Diabetes insipidus (Beobachtungen am Patienten und Implantationen von Tierischen und menschlichen Hypophysen) Wien klin Wochnschr 1937 L -29

441a AZERAD E Sur le traitement du diabete insipide par des implantations de fragments de lobe posterieur d hypophyse fraiche Bull et Mem Soc med Hop de Paris 1946 LXII 279

44 McCONNELL A A A case of diabetes insipidus influenced by partial thyroidectomy Irish Jour Med Sci 1936 (Dec) p 74

458 HARVEY A A case of diabetes insipidus permanently cured by an intercurrent attack of measles Birmingham Med Rev 189 XXXI 166

459 ELLIS C H and WIERSMA C A G Influence of electronarcosis on secretory activity of the pituitary gland Proc Soc Exper Biol and Med 1945 LVIII 160

460 DROULT, P L, VERAIN, M, GRANDPIERRE G and PIERQUIN Un cas de diabete insipide avec glycosurie traitement par les ondes courtes sur la region hypophysotuberienne Bull et Mém Soc med d Hop de Paris 1936 LII 115

461 JUDSON, W E EPSTEIN F H TINSLEY C M, BURROWS B A and WILKINS R W The hemodynamic and renal functional effects of venous congestion of the limbs in patients with diabetes insipidus Jour Clin Invest in press

462 WILKINS R W CULBERTSON J W BURROWS B A TINSLEY C M JUDSON W E and BURNETT, C H Antidiuresis and renal vasoconstriction following venous congestion of the limbs in normal hypertensive and splanchnicectomized subjects Jour Clin Invest, 1949 XXVIII 819

463 BARTSOKAS S A Propos d une cas de virilisme surrenal avec tumor de la corticale surrenale et diabete insipide chez une fillette de 8 mois Arch franç Pediat 1947 IV .66

464 RALLI, E P ROBSON, J S, CLARKE D and HOAGLAND C L Factors influencing ascites in patients with cirrhosis of the liver Jour Clin Invest 1945 XXIV 316

465 EVERSOLE W J BIRNIE J H and GAUNT R Inactivation of posterior pituitary antidiuretic hormone by the liver Endocrinology 1949 L 378

466 PORTER R J and MILLER R A Diabetes insipidus following closed head injury Jour Neurol Neurosurg and Psychiatry 1948 XI 58

467 MUSSIO FOURNIER J C and SARALEGUI J P Laurence Moon Biedl Syndrome avec Diabete insipide maladie de Legg Perthes et Doight de Telford Smith Bull et Mem Soc Med d Hop de Paris 1948 LXIV 34

468 DANCIS, J BIRMINGHAM J R and LESLIE S H Congenital diabetes insipidus resistant to treatment with pitressin, Am Jour Dis Child, 1948 LXXV 316

469 FALTA W and TITZE H Behandlung des Diabetes insipidus mit Weckmitteln Wien klin Wochnschr 1949 LXI 164

470 WINTER J A Diabetes insipidus amelioration after tonsillectomy, Am Jour Pediat 1948 XXXII 78

Skin

Much interest is attached to the somewhat varied but important cutaneous manifestations in Hodgkin's disease[8, 39, 59]. Goldman[39] records involvement of the skin in 38 per cent of his cases but the skin was affected in one manner or another in only 33 or 18.7 per cent of our patients. Pruritus is a common and extremely annoying symptom. It often comes early or even precedes the glandular swelling but it may appear at any time during the course of the disease and persist with great tenacity. There seems to be no direct connection between the pruritus and the enlargement of lymph nodes; at times the itching increases in intensity during exacerbations of the disease. As a rule it is generalized and almost unbearable. It is commonly thought to proceed from the action of some toxic substance elaborated during the course of the disease. Pigmentation of the skin used to occur after the prolonged use of arsenic as a therapeutic measure and is one of the results now of irradiation therapy but exclusive of these causes a brownish discoloration of the skin or mottling, usually associated with involvement of the abdominal lymph nodes, sometimes is seen. In one group of cases the brownish discoloration affects principally the normally pigmented areas and there may only be a deepening of color over the eyelids, the axillae, the nipples, the pubis and genitalia. Areas of the skin that are subject to irritation are also likely to be darkened. In another group of cases a brownish pigmentation appears in irregular blotches about the chest and abdomen giving the skin a pie bald appearance. In a third group the pigmentation is uniform as it may be in Addison's disease and the patient gradually darkens in complexion.

Occasionally urticaria and localized edematous swellings appear. An irregular pustular dermatitis which may or may not follow irritation of the skin by scratching is seen in some patients (Fig. 8). Hemorrhages in the skin have been seen but they are certainly far less frequent than in leukemia. Exfoliative dermatitis has been noted as a rare complication. A scarlatiniform rash was seen in one of our patients. Herpes zoster is a painful and persistent complication. It is considered to be dependent upon extension of the granulomatous growths to the spinal nerve roots. It may be hemorrhagic and frequently leaves a scar on healing. The skin may be the seat of actual granulomata (Fig. 9) and cases have been reported in which these were the earliest manifestations of the disease[34(a), 59]. They form nodules or plaques of various sizes occurring sparsely or in considerable numbers. As a rule the surface of the nodules tends to ulcerate. Frequently they have been confused with cutaneous tuberculids and with mycosis fungoide which by some is supposed to resemble very closely Hodgkin's disease of the skin. In some instances, as occurred in one of our cases, the lesions involve the skin of the entire body and produce the appearance of generalized lymphomatosis cutis

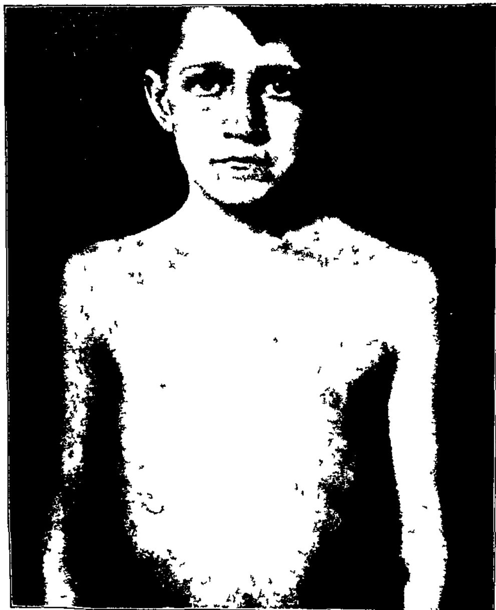


FIG 8 F K after operative and x ray treatment showing irregular eruption over body



Fig 9 M A age 28 showing nodule in the supraclavicular area and in the breasts with two subcutaneous nodules that have broken through the skin and become infected

Genitourinary System

The occasional involvement of the kidneys in Hodgkin s disease is rarely if ever detected during life Albumin may be observed In one of our patients who showed extensive osseous lesions large quantities of Bence Jones protein were constantly present in the urine An instance of Bence Jones proteinuria occurring in a patient with extensive deposits of granulomata in the kidney but without mention of bone involvement has also been recorded[40] Hematuria occurred in 2 patients When there is extensive disease of the retroperitoneal or pelvic lymph nodes one or both ureters may be compressed giving rise to unilateral or bilateral hydronephrosis This took place in 1 of our patients In 1 other case the ureter itself was invaded by lymphomatous tissue

The presence of granulomata in the mucosa or wall of the urinary bladder is very rare but was found at autopsy in one of our cases The testicles, epididymis

and ovaries are rare seats of Hodgkin's disease In one of our autopsies a localized granulomatous mass was discovered in the vagina

Other Organs

The voluntary muscles are invaded not infrequently particularly by Hodgkin's sarcoma This occurs most often perhaps as an extension from the retroperitoneum into the psoas and iliac muscle but also takes place in the pectoral muscles

The diaphragm is not a very unusual place for the deposit of secondary granulomata as was found to be the case in 3 of our autopsies Granulomata in rare instances are found in the breast In 1 of our patients there was iritis and in 2 hemorrhagic retinitis which probably was associated with a severe anemia

The thyroid gland the pancreas the adrenals and the pituitary have been noted to contain granulomata Symptoms referable to these organs have however rarely been described although diabetes insipidus has been recorded[57] as already noted

Constitutional Symptoms

The profound constitutional symptoms that form a part of this disease are of great importance and impart a characteristic aspect to the course of the disease They are often present from the very start In the early stages and sometimes even before there is notice enlargement of the lymph nodes patients are prone to complain of loss of weight undue fatigue malaise anorexia or unexplained night sweats As the disease progresses these features become more and more prominent so that during the later stages there is extreme exhaustion and actual emaciation These symptoms often are accentuated by pallor and the intolerable itching of the skin Even without fever the basal metabolic rate tends to rise and was above +20 in 6 of 10 of our patients in which it was determined In one of these it was +52 in another +65 Many patients present a peculiar pallor of the skin and this may be present in the absence of a severe grade of anemia

These and other constitutional symptoms are not necessarily proportional to the extent of the granulomatous lesions for they often progress in spite of the fact that the tumors are kept under control by x ray or radium therapy The disease may terminate fatally, and at autopsy one may find only insignificant enlargement of lymph nodes and few or no secondary growths in other organs In the later stages of the disease the patients may present the cachectic appearance of one dying of cancer or when fever leukocytosis and anemia are all present the picture of an intractable progressive, chronic infection

Fever

Most patients have fever sometime during the course of the disease During the early stages however fever is uncommon although it occurred as a premonitory symptom in 24 or 14 2 per cent of our 176 patients When however the swelling of lymph nodes is confined to the neck or axilla and particularly in Hodgkin s paragranuloma fever is rarely if ever present during the early phase Fever appears to be much more common at all stages of the disease when the thoracic or abdominal nodes are affected In this group of patients unexplained fever accompanied by loss of weight and asthenia may be the only evidence of disease for weeks or months An interesting feature of these prodromata is that they may be intermittent with extended remissions

There is great variation in the temperature curves In one class of cases there is a continued mild fever slightly irregular varying a few degrees and rarely exceeding 101° or 102° F (Fig 10) This slight rise of temperature may persist

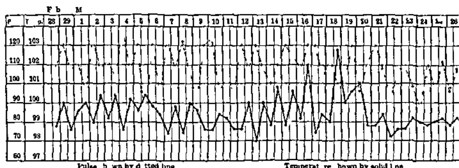


Fig 10 Chart of M S (Fig 4) February 1916 moderate and fairly constant fever

for months or even longer and in certain cases lasts throughout the course However more often during the later stages the character of the temperature curve changes to one of three other types In the first group of cases the temperature is quite irregular high and intermittent showing perhaps diurnal remissions of several degrees with afternoon rises (Fig 11) With the elevation of temperature there may be chilly sensations or actual chills and sweats even when there is no secondary infection During these periods the patients frequently experience pain of more or less severity either in the abdomen or in the extremities In the second group which comprises about 10 to 20 per cent of cases and occurred in 34 or 19 3 per cent of our series the type of fever is exceedingly interesting It is relapsing in character and shows periods of pyrexia of several days or even weeks duration alternating with longer or shorter periods of apyrexia (Figs 12 and 12(a)) This condition may continue for many months or as it did in one of our cases for over

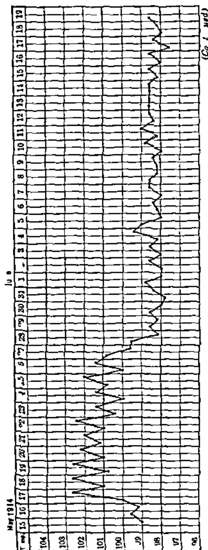
Pulse shown by dotted line

Temperature shown by solid line

(Continued)

Pulse shown by dotted line

Temperature shown by solid line



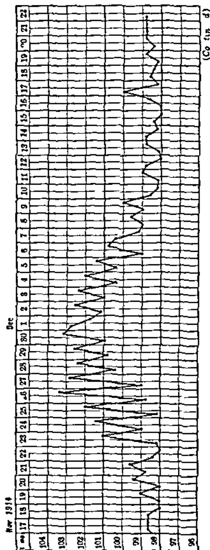


FIG 12 For legend see next page whe e remainder of chart appears

Nov 1917 ... Dec

Pulse shown by dotted line

Temperature shown by solid line

(Continued)

Jan 1918 ... Feb

Pulse shown by dotted line

Temperature shown by solid line

T m e a u e ha of I C (F g) howing na k lly i regula by w ng ng v w h ap p ea a e

5 years During the febrile periods there is a tendency for the lymph nodes to increase rather rapidly in size In some cases the pyrexia has been accompanied by an acute enlargement of the spleen Murchison[61] drew attention to these relapsing fevers in Hodgkin s disease and later Ebstein[62] and Pel[63] described cases illustrating a condition in children to which Ebstein first gave the name of chronic relapsing fever Pel and later Ebstein too decided that these cases were examples of Hodgkin's disease showing this curious type of relapsing fever which by some has been called Pel Ebstein Fever Since then it has been suggested that in such cases the rise in temperature is due to an infection of some variety but there has been no evidence to substantiate this theory Ruffin[64] has reported a case with 4 relapses in which during the periods of pyrexia blood cultures showed no growth Many other observers have had similar experiences This entire group of cases has been well discussed by McNalty[65] and by Whittington[66]

In the third type which resembles somewhat the relapsing fever the temperature undulates never reaching normal but rising in waves to 102 to 104° F for days or weeks This perhaps is the most unusual form and occurred in only 17 or 9 6 per cent of our cases

In both the relapsing and undulating forms of fever the patient although unaware of a high temperature, feels miserable often notices increase in pain and in the size of the nodes feels nauseated and sometimes vomits The leukocyte count may rise or may fall and very often the anemia when present, increases With the subsidence or disappearance of fever all of these symptoms may improve or be entirely relieved but only to return with subsequent rises of temperature

Blood

The hematological alterations are so irregular that they are unpredictable and have proved of little or no diagnostic value Due to these very reasons however they lend a distinctive character to this disease The change that take place as Hodgkin s disease progresses are apt to be somewhat excessive at times almost dramatic and often have an important bearing on the symptomatic treatment of the patient

In the early stages of the illness and particularly in paragranuloma, there is no anemia and when the enlargement of lymph nodes is restricted to local groups the red blood cells may remain within normal limits for years even though the patient presents a certain degree of pallor On the other hand when the process advances rapidly or reaches the later stages of Hodgkin s disease an anemia of very severe grade is common but not invariable This anemia may assume one of several forms It may be normocytic microcytic hypochromic or in rare instances macrocytic in type Not uncommonly in such cases the hemoglobin

June 1919

Sept 1919

Continued

Oct 1919

Nov

Fig 12(a) Temperature chart of F M showing relapsing type of fever over a period of five years The disease was largely confined in this patient to the nodes of the abdominal cavity and to the spleen There were many other febrile exacerbations that are not included in this chart

stages this is often the situation although exactly the reverse may be true Thus in 20 of our 60 fatal cases the leukocytes were over 10 000 and in 7 of these above 20 000 While in 13 the leukocytes fell below 5 000 and were often as low as 1 000 to 2 000

Attention has been called frequently to the pronounced eosinophilia that occasionally is observed in Hodgkin s disease This is not very common The eosinophilic leukocytes of the blood rose above 4 per cent in only 41 of our cases in 5 of these the eosinophiles ranged from 20 to 35 per cent Eosinophilia was seen particularly in the fatal cases occurring in 12 of 60 patients Occasional instances are however on record in which the eosinophilia has been excessive[70 71] and Stewart[7] has reported a case in which the eosinophiles formed from 70 to 90 per cent of the extraordinarily high total number of 100 000 to 125 000 leukocytes

The blood platelets may be increased but they are generally present in the usual numbers The sedimentation rate has been found elevated in a large proportion of cases of Hodgkin s disease[73] This may fluctuate rising with exacerbations of symptoms and falling to normal with remissions In 37 of our patients the sedimentation rate (Wintrobe) was above 20 and in 7 of these above 50 The increased rate shows a peculiarity that distinguishes it from the blood of patients with tuberculosis and acute infections for Koster[74] has found that the sedimentation rate of citrated blood from normal individuals and from patients with a wide variety of infections including tuberculosis decreases to zero or to low figures after preservation in vitro for 24 hours whereas the rate is maintained at the same figure or even increases at the end of this period in persons with malignant growths and Hodgkin s disease *The observation has been confirmed by Feldman*[75] who considers that this test may be of diagnostic value

Course

The course of the disease is so irregular and the changes as it progresses are so frequent and assume such bizarre forms that it is almost impossible to predict what will happen during its fluctuations from onset to final outcome Efforts have been made to separate from the conglomerate picture certain forms of the disease Ziegler[8] has described 11 more or less distinct types namely the form with acute course the localized form the generalized form the type with mediastinal tumor the larval or typhoid form the osteoperiostitic form the intestinal type the Mikulicz type and the form resembling mycosis fungoides These designations might very well reflect the situation in any one patient at a given time and are possibly useful as an indication of the predominant features that may characterize the multiform disease in the different stages but they scarcely give a comprehensive view of the diversity of symptoms and signs which alter from

falls to 30 or 40 per cent and the red blood cells to between 3 and 4 million An anemia of this degree developed in 44 of 141 of our cases in which the red blood cells were counted Occasionally the anemia is of an extreme grade The red blood cells fell below 1,000 000 in 6 of Jackson and Parker's[1] patients ranged between 1 and 2 million in 9 of our patients and dropped below 1 000,000 cells in 2 cases Although such severe degrees of anemia are seen usually in the terminal stages some patients in whom the disease is fatal, never develop any anemia at all In 11 of our 60 fatal cases in which blood counts were made the hemoglobin remained above 80 per cent and the red blood cells above 4 million but in 15 cases the hemoglobin ranged between 60 and 80 per cent in 15 between 40 and 60 per cent in 12 between 0 and 40 per cent in 4 between 10 and 20 per cent, in 1 below 10 per cent The red blood cells were between 3 and 4 million in 23 patients, between 2 and 3 million in 13 between 1 and 2 million in 7 and below 1 million in 1 One patient in whom the disease lasted 2 years and in whom at autopsy miliary granulomata were found widely distributed through many organs as well as in the marrow of many bones was thought to have died of aplastic anemia The hemoglobin sometime before death remained at 20 per cent the red blood cells at 1 000 000 and the leucocytes at 1 050

Several instances are reported in which hyperchromic macrocytosis[67] has occurred, but whether this is due to an increase in reticulocytes or to a more fundamental change in maturation of erythrocytes is uncertain In a few instances hemolytic anemia of considerable severity accompanied by an excessive number of reticulocytes has been reported

The leucocytes are subject to great variations In the early phases and in the localized forms of Hodgkin's disease the total numbers are often within normal limits The count lay between 5 000 and 10 000 in 63 of 134 of our patients in which counts were made Occasionally however there may be a slight leukopenia As the disease progresses a leukocytosis is the rule At least 48 of our patients had quite consistently leukocyte counts between 10 000 and 20 000 and 21 had leukocyte counts above 20 000 At times the leukocytosis may be excessive for Bunting[68] describes 1 case of 2 years duration in which the leukocytes were 100 000 On the other hand instances of excessive and prolonged leukopenia have been recorded[69] In 2 of our 134 patients the leukocyte count dropped below 1 000 cells in 1 case to 550 In a number of instances leukopenia is undoubtedly the result of x ray treatment and through this means a pronounced leukocytosis may be converted into an alarming leukopenia

Although the differential leukocytic formula is of interest it has not proved, as Bunting[68] suggested to be of diagnostic value The lymphocytes and monocytes may be relatively increased during the early phases in those patients who have a moderately low total leukocyte count but as a rule even at this time, the polymorphonuclear neutrophiles predominate In the progressive and advanced

pyogenic organism such as streptococci and staphylococci are not unknown This complication arose in 4 of our patients 2 of whom died of general infections by hemolytic streptococci 4 patients died of pneumonia 1 of lung abscess secondary to bronchial obstruction from granulomata One died of meningitis 1 with duodenal ulcer died with acute intestinal obstruction 1 succumbed to exploratory craniotomy performed for suspected brain tumor and 1 died primarily from tracheal obstruction due to stenosis from invading granulomatous tissue

Diagnosis

It may be said once and for all that at the present time the only means of making an accurate diagnosis of Hodgkin s disease is by the microscopic examination of an excised lymph node or other granulomatous tissue Precautions must be taken even when this method is employed The node should be carefully selected fixed immediately and cut in thin sections properly stained for histological study If these procedures are properly performed little difficulty is encountered in arriving at a definitive conclusion Material obtained by puncture of a lymph node or of the bone marrow is rarely satisfactory for diagnostic purposes The Gordon test is positive in about 70 per cent of cases of Hodgkin s disease but it is not specific

From the clinical history and physical examination alone one can be led to suspect Hodgkin s disease in a considerable proportion of cases When there is enlargement of superficial lymph nodes affecting single groups particularly those in the neck or when there is enlargement of multiple groups especially if these are irregular in size and distribution one should always consider the possibility of Hodgkin s disease whether or not the process is accompanied by the premonitory symptoms that are so often noted in lymphogranulomatosis

Localized enlargements are confused most often with tuberculous lymphadenitis swellings secondary to infected tonsils or teeth tularemia brucellosis rat bite fever infectious mononucleosis syphilis sarcoid carcinomatous metastases or one of the different forms of lymphosarcoma

Since tuberculous adenitis is one of the commonest of these conditions it is often puzzling to know whether the patient is suffering from Hodgkin s disease or tuberculous lymphadenitis Usually the final conclusion cannot be arrived at without biopsy A history of previous tuberculous infection sometimes is helpful and it should be remembered that the negro is highly susceptible to tuberculosis and relatively insusceptible to Hodgkin s disease Some aid may be obtained from the condition of the nodes themselves The tuberculous glands are often firm usually matted together as a rule deep seated in the neck beneath the sternocleido mastoid muscle and frequently tender They may be adherent to the skin which is reddened or there may be small sinuses or scars left by discharging nodes

time to time the clinical picture of the disease Possibly the simplest and most satisfactory division of cases is that proposed by Jackson and Parker[15] who base their classification both upon distinctive pathological alterations and differences in the clinical pictures

The first of the 3 types, which they recognize, namely Hodgkin s paragranuloma is apparently a benign and infrequent form localized usually to isolated groups of nodes such as those of the neck axillae or inguinal regions persisting or relapsing over long periods and sometimes lasting for years Rapid extension to other nodes or to the internal organs does not occur unless the lesion changes as it may do in some instances to the second form or granuloma

Hodgkin s granuloma is the commonest and most familiar form of Hodgkin s disease The progress of Hodgkin s granuloma may be rapid or protracted over 4 or 5 years or longer It is characterized by the formation of multitudinous tumors affecting superficial and deep lymph nodes the spleen liver bones lungs and abdominal viscera Its progress is attended by the most diverse manifestations which may attract the attention of the observer to any of the superficial or deep regions mentioned by Ziegler and others When the disease is restricted, as happens in about 10 per cent of cases to the deep nodes and internal organs the clinical picture takes on the character of an obscure chronic infection or of a neoplasm

In the third type or Hodgkin s sarcoma the peculiar granuloma assumes the definite qualities of a new growth for this form of the disease affects most frequently elderly people has a tendency to arise in the deep nodes invades tissues and neighboring organs and runs a rapid course ending invariably in death within a year or two

Although complicating circumstances may affect the course of all forms of Hodgkin s disease they do not appear to be particularly common in any type Pregnancy seems to have little affect on Hodgkin s disease or Hodgkin's disease upon pregnancy[76 77] Goldman and Victor[39(b)] encountered 11 instances of pregnancy in their total series of 319 cases in 7 of these the women were carried to term in 3 a therapeutic abortion was performed, and in one a miscarriage took place

The combination of Hodgkin s disease and tuberculosis is fairly common occurring in from 5 to 25 per cent of reported cases Chronic lesions may be discovered at autopsy in the lungs and other organs or more rarely tuberculosis may be present in an active state One of our patients was found at autopsy to have generalized miliary tuberculosis 1 scattered tubercles through many organs 2 chronic pulmonary tuberculosis and 1 a solitary tubercle in the small intestine making a total of 5 instances of tuberculosis or something less than 12 per cent in our 42 autopsies

One of our patients had diabetes mellitus 1 had survived a recent severe attack of acute hemorrhagic nephritis Secondary infections of the lymph nodes by

metastasize to the cervical lymph nodes Even in sections of these tumors the collections of cancerous cells may be sparse and the hyperplasia of lymphoid tissue so noticeable that it resembles in some respects Hodgkin s disease New growths of the thyroid have been mistaken for Hodgkin s disease

Where the enlargement of lymph nodes is generalized or when the spleen is noticeably enlarged Hodgkin s disease bears superficial resemblances to one or another variety of leukemia Careful study of the blood will however leave no doubt as to the diagnosis of leukemia Extensive involvement of the skin which may appear early in the disease can scarcely be distinguished from the generalized infiltrations produced by lymphatic leukemia The nodular lesions may be mistaken for mycosis fungoides Involvement of the bones may suggest tuberculosis or tumor metastases and an extension from the skull to the dura or to the brain has led to the diagnosis of brain tumor

The recognition of Hodgkin s disease becomes extremely difficult or impossible when the granulomatous growths are restricted to the thorax or abdomen This occurs in about 10 per cent of all patients Growths in the thorax often are mistaken for mediastinal tumors of one sort or another sometimes for aneurysm and frequently for carcinoma of the lung Eleven of our patients were of this type With involvement of the retroperitoneal and abdominal nodes in the absence of any significant enlargement of superficial lymph nodes there may be nothing to give a clue as to the true nature of the disease This occurred in 25 per cent of our 176 patients Such cases have been mistaken for typhoid fever appendicitis tuberculous peritonitis abscess of the liver undulant fever dysentery obscure abdominal infections or new growths particularly of the gastrointestinal tract In the unusual instances of granuloma of the stomach the diagnosis of carcinoma or peptic ulcer often has been made

Since some of these patients develop severe grades of anemia they may be thought to have aplastic or refractory anemia or if the spleen is much enlarged Banti s disease or splenic anemia Jaundice which is comparatively common in this group leads to the suspicion of cholelithiasis, cirrhosis of the liver or new growth of the biliary tract

Unless superficial lymph nodes become involved during the course of the disease in this group of patients exploratory laparotomy may be the only method of arriving at a correct diagnosis It is a mistake to employ laparotomy as a last resort It should be performed early A few months after the onset of abdominal symptoms an exploratory operation was done in one of our patients A mass of mesenteric lymph nodes was removed A conclusive diagnosis of Hodgkin s disease could then be made and x ray therapy instituted after which the patient has been free from any evidence of disease for over 2 years

Hodgkin s disease may pursue a very rapid course in many of these patients in whom the lungs or abdominal organs are extensively involved The acute

A roentgenogram sometimes is useful since the presence of areas of calcification in the nodes is indicative of tuberculosis Great confusion may result when the mediastinal and bronchial nodes are affected or when the roots of the lungs are involved Under such circumstances a negative tuberculin reaction is helpful in excluding tuberculosis In uncomplicated Hodgkin s disease the skin is quite refractory to tuberculin In the last analysis however, it will be necessary to resort to a biopsy for diagnosis

Chronically infected lymph nodes most familiar in children habitually sub side of themselves when the focus of infection is removed

The history and clinical course of the disease in tularemia and brucellosis to gether with the bacteriological and immunological examinations should allow one to eliminate these infections from consideration The same may be said of rat bite fever Syphilis may lead to confusion when the epitrochlear axillary in guinal or femoral lymph nodes are enlarged An enlargement of the axillary nodes following an extragenital chancre of the fingers may be mistaken for Hodgkin s disease as happened to one patient sent to us with the latter diagnosis Confusion may arise also in differentiating infectious mononucleosis from Hodgkin s disease At least 2 patients suffering from infectious mononucleosis have been sent to us with a diagnosis of Hodgkin s disease and with a hopeless prognosis At the pres ent time repeated differential leukocyte counts and the presence of heterophile antibodies in high titer should prevent such an error

It is often extremely difficult to differentiate lymphatic sarcoids from Hodg kin's disease particularly when the typical lesions of sarcoid are not found in the skin the structures of the eyes or the bones Both diseases are prone also to affect the mediastinal and bronchial lymph nodes as well as the lung The roentgeno-grams of the chest may be similar, but sarcoid is much more likely to produce filmy shadows through the parenchyma of the lungs than does Hodgkin's disease

It is usually impossible to differentiate Hodgkin s disease from many of the forms of lymphosarcoma without a histological examination of tissue There are, however minor features that have some value in differentiating the two diseases[78] It has been pointed out frequently that lymphosarcoma is much more likely to affect the tonsils and gastrointestinal tract than does Hodgkin s disease On the other hand pruritus undulating and relapsing fever and pronounced poly morphonuclear leukocytosis sometimes with eosinophilia are common in Hodg kin s disease but rare or absent in lymphosarcoma The spleen is affected in a large proportion of cases of Hodgkin s disease but except for the cases of follicular lymphoblastoma escapes almost uniformly in lymphosarcoma The clinical similarity between Hodgkin s sarcoma and reticular cell lymphosarcoma is ex tremely close

Carcinomatous metastases to lymph nodes are often confounded with Hodg kin s disease This is especially true of the rare nasopharyngeal growths that

of lack of information it has not been possible to differentiate our cases into the 3 types described by Jackson and Parker Therefore our series as well as those of other observers are not exactly comparable to those of Jackson and Parker

The following table (Table III) is taken from the papers of Jackson and Parker to which have been added our own figure It has already been pointed out that the patients who have few constitutional symptoms and in whom the disease is limited to individual groups of superficial lymph nodes particularly those in the neck live longest while those in whom the disease spreads rapidly attacking the thoracic and abdominal organs and producing a train of constitutional symptoms live for only a few months or at most a few years

TABLE III

DURATION OF HODGKIN S DISEASE FROM ONSET TO DEATH

Duration in years	Jackson & Parker (136 cases of granuloma)	Uddestromer (494 cases unclassified)	Longcope (65 cases unclassified)
Less than 1 yr	24%	33%	20 %
1-2 years	45%	45%	37 %
3-4	17%	16%	24 6%
5-9	13%	6%	10 7%
10 years +	1%	0	6 1%
Unknown	0	0	1 6%
	100%	100%	100%

TREATMENT

There is no specific treatment for Hodgkin s disease Symptomatic or palliative therapy can be considered in four categories First drugs and chemicals secondly surgery thirdly hypothetical antisera and vaccines and fourthly irradiation

(1) Preparations of arsenic have been employed in the treatment of Hodgkin s disease for years Fowler s solution and sodium cacodylate have been used most generally but arsenic has much less effect upon Hodgkin s disease than upon the leukemias It is sometimes beneficial to administer arsenic between the courses of irradiation therapy In some patients arsenic relieves to a certain extent the intolerable itching Iron and liver extract produce no effect upon the anemia Transfusions are however of temporary benefit

Derivatives of mustard gas known as nitrogen mustards which have been developed during the war have been found to be remarkably destructive to lym

phase of the disease accompanied by symptoms may last only 4 or 5 weeks When the lungs are the seat of granulomata, the disease runs its course within 1 year or at most 2 years On the other hand a few of the patients having involvement of the abdominal organs and lymph nodes may live for several years

Some idea of the difficulty in diagnosis in these patients suffering from the thoracic or abdominal type of Hodgkin s disease may be gained from the fact that 1 of our patients was suspected of having carcinoma of the lung 1 esophageal stricture, 2 liver abscesses 2 cholelithiasis 1 carcinoma of the gastrointestinal tract, 1 duodenal ulcer 1 rheumatic fever 1 pyelitis 1 polyserositis, 1 aplastic anemia and 2 brain tumor Erroneous diagnoses quite as varied as these have been recorded by many observers It is therfore important to recognize the fact that Hodgkin s disease may mimic symptomatically a wide variety of abnormalities

Prognosis

It is probable that practically every case of Hodgkin's disease terminates in death The average duration of life after the advent of symptoms usually is given as 3 years but in accordance with other characteristics of this peculiar affection there are outstanding exceptions to this statement Death may occur in fulminating cases within a few weeks of onset or on the other hand patients may still be alive 18 to 20 years after the first appearance of enlarged lymph nodes One of our patients died 5 weeks after the first signs of illness and one is calculated to have had the disease 20 years before death supervened Twelve of our 65 patients died during the first year of illness 24 between the first and second years and 11 between the 2nd and 3rd year Thus 72 6 per cent of the 65 deaths took place within 3 years of onset On the other hand 7 of the 65 fatal cases are known to have lived for more than 6 years One of these lived 10 years, 1 probably 12 years and 1, 20 years All of these patients were treated by some form of irradiation

Among the patients who were still living when last observed 13 had had the disease for more than 5 years This figure amounts to 11 7 per cent of the 111 still alive at that time Two patients had suffered from the disease for 9 to 10 years, 1 for more than 13 years and 2 for 15 years All of these patients had been treated by x ray or radium

It is highly probable that most of the patients who survive over many years are instances of paragranuloma which if they progress to granuloma do so a comparatively short time before death Jackson and Parker[15] state that 54 per cent of their 6 cases of paragranuloma were alive and free from symptoms more than 5 years after onset while 5 of the 26 survived a 15 year period The majority of the 12 patients who died succumbed after a transition to granuloma On account

of lack of information it has not been possible to differentiate our cases into the 3 types described by Jackson and Parker Therefore our series as well as those of other observers are not exactly comparable to those of Jackson and Parker

The following table (Table III) is taken from the papers of Jackson and Parker to which have been added our own figure It has already been pointed out that the patients who have few constitutional symptoms and in whom the disease is limited to individual groups of superficial lymph nodes particularly those in the neck live longest while those in whom the disease spreads rapidly attacking the thoracic and abdominal organs and producing a train of constitutional symptoms live for only a few months or at most a few years

TABLE III

DURATION OF HODGKIN S DISEASE FROM ONSET TO DEATH

Duration in years	Jackson & Parker (136 cases of granuloma)	Uddestromer (494 cases unclassified)	Longcope (65 cases unclassified)
Less than 1 yr	24%	33%	0 %
1–2 years	45 %	45%	37 %
3–4	1 %	16%	24 6%
5–9	13%	6%	10 7%
10 years +	1%	0	6 1%
Unknown	0	0	1 6%
	100%	100	100%

TREATMENT

There is no specific treatment for Hodgkin s disease Symptomatic or palliative therapy can be considered in four categories First drugs and chemicals secondly surgery thirdly hypothetical antisera and vaccines and fourthly irradiation

(1) Preparations of arsenic have been employed in the treatment of Hodgkin s disease for years Fowler s solution and sodium cacodylate have been used most generally but arsenic has much less effect upon Hodgkin s disease than upon the leukemias It is sometimes beneficial to administer arsenic between the courses of irradiation therapy In some patients arsenic relieves to a certain extent the intolerable itching Iron and liver extract produce no effect upon the anemia Transfusions are however of temporary benefit

Derivatives of mustard gas known as nitrogen mustards which have been developed during the war have been found to be remarkably destructive to lym

phoid tissue Tentative trials have been made in the treatment of leukemia, lymphosarcoma and Hodgkin s disease with these chemicals[79 80 81] Two preparations have been used These are tris (B chloroethyl) amine hydrochloride and methy bis (B chloroethyl) amine hydrochloride Details of the results obtained in the treatment of one group of 27 cases of Hodgkin s disease have been described by Goodman, Wintrobe and their associates[8] and of a second group of 27 cases by Jacobson Spurr and their associates[83] Rhoads[81] in a summary of the effect produced by these chemicals emphasizes their high toxicity which is directed in particular against the hematopoietic system In many patients intravenous injections of the chemical brought about remission of symptoms and reduction in size of the tumor masses This improvement was sometimes dramatic and lasted for weeks or months Exacerbations were the rule but these again responded favorably to treatment It was repeatedly observed that patients who had become resistant to x ray therapy responded favorably to injections of methy bis (B chloroethyl) amine hydrochloride It is certain that the nitrogen mustards employed up to the present time are not curative and that the use of the chemicals is attended by danger since the margin between the toxic and therapeutic dose is narrow and yet it may prove that these or other similar preparations will find a place in the treatment of Hodgkin s disease

(2) Operative treatment which at one time was in vogue has largely been abandoned for partial removal of granulomatous glands usually is followed by rapid recurrence, and complete resection of all diseased tissue is almost impossible There is however something to be said for the type of operation that was insisted upon by Yates[84] This consisted in the accurate dissection of all lymph nodes in a locally diseased area Quite recently Slaughter and Craver[85] who have had extensive experience in the use of x ray advocate quite strongly the preliminary complete resection of nodes when the disease is localized followed by x ray treatment

(3) Attempts have been made to use emulsions of Hodgkin s disease nodes as autogenous vaccines[86], sensitized vaccines of hypothetical elementary bodies[28] or sera from animals presumably immunized against them and the serum of chickens injected with mash of ground lymph nodes from patients with Hodgkin's disease[87], but none of these methods has proved sufficiently successful to warrant their general adoption Occasional brilliant temporary improvement has been recorded such as that described by Gascoin[88] after injections of toad venom, but such results are often unpredictable and unreproducible

(4) The one method of therapy that is known to result often in dramatic symptomatic improvement in many patients is irradiation either by x ray or radium This form of treatment was introduced about 1900 and has been employed extensively since that time[89 90 91 85 92] Desjardin[92] has pointed out that survival depends chiefly upon three factors namely (1) the relative acuteness or chronicity of the malignant lymphoid process (2) the extent of involvement and the stage,

which the condition has reached when it is recognized and when treatment is started and (3) the thoroughness and care with which the treatment is planned and given The technique of treatment varies somewhat in the hands of different radiologists As a rule 200 to 250 kilowatts are used for irradiation The total dosage in the course of several treatments varies from 600 to 1 200 r In the hands of experts injury does not occur to the skin Caution must be exercised in irradiation of the mediastinum and chest for a deleterious effect may be produced upon the normal lung tissue resulting in an irradiation pneumonitis [92] It was thought at autopsy that this had occurred in one of our patients Application of x ray over the abdomen is very likely to produce irradiation sickness characterized by fever chills abdominal pains nausea and vomiting These results are unpleasant but usually not dangerous

Since irradiation has been employed as the treatment of choice for many years in almost all cases of Hodgkin s disease it is extremely difficult to gage the influence of this therapy on the actual duration of life for there are few or no modern control observations There is no question as O Brien[91] points out that the symptomatic effect is highly beneficial and in many cases life saving and it also seems assured that if life is prolonged the patient is capable of leading a comparatively normal existence for many years This only occurs however in a small proportion for 40 of his 60 patients or 66 6 per cent lived less than years On the other hand 15 or 20 5 per cent lived 2 to 6 years 5 lived on an average of 9 years and 1 lived for o years Slaughter and Craver[89] state that 17 7 per cent of their 265 cases survived at least 5 years following treatment and 3 4 per cent lived for more than 10 years 1 patient living 18 years 1 16½ years and 1 probably 33 years Gilbert[90] reports a survival time of more than 3 years in 45 7 per cent of his cases and more than 5 years in 34 per cent Jackson and Parker[1] found that 17 of their 35 patients or 47 per cent who were still alive on January 15 1945 had survived for 5 years and state that 16 per cent of their entire series that had received systematic treatment by irradiation lived for more than 5 years

One must conclude therefore that the disease is held in abeyance very frequently by x ray treatment and that an occasional patient although perhaps not actually cured is restored to health for an almost indefinite period of time

The use of radioactive isotopes to replace x ray in the treatment of Hodgkin s disease is of such recent date that no definite conclusion can be drawn from the few published reports but according to Reinhard and his associates[94] radioactive phosphorus or P^{32} is inferior to x ray in the treatment of Hodgkin s disease On the other hand Hahn and Sheppard[95] who have treated patients with Hodgkin s disease by intravenous injections of radioactive manganese or M^{n} in a colloidal state have noted distinctly favorable results evidenced by reduction in size of lymph nodes and remission of fever They are inclined to believe that this preparation is more effective than radioactive phosphorus

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BIBLIOGRAPHY

1 HODGKIN TH On some marked appearances of absorbent glands and spleen Trans Medico-Chirurg Soc London 1832 XVII 68

2 ROLLESTON H D Some aspects of lymphadenoma (Hodgkin s disease) Practitioner 1911 I

3 FOX H Remarks on presentation of microscopical preparations made from some of original tissue described by Thomas Hodgkin 183 Guy s Hosp Report 1936 LXXXVI 11

4 WILKS S Cases of lardaceous disease and some allied affections with remarks Guy s Hosp Report 1856 II 103

5 WILKS S Cases of enlargement of lymphatic glands and spleen (or Hodgkin s disease) Guy s Hosp Report 1865 XI 56

6 STERNBERG C Über eine Eigenartige unter dem Bilde der Pseudo-leukamie verlaufende Tuberkulose der lymphatischen apparatus Zeitschrft fur Heilkund 1898 XIX 21

6(a) STERNBERG C Universelle Primarekrankungen des lymphatischen Apparatus Centralbl f d Grenzgebiet d Med und Chir 1899 II 641 711 770 813 and 847

6(b) STERNBERG C Primarekrankungen des lymphatischen und haematopoietischen Apparatus Eigenartige under dem Bilde der Pseudo leukamie verlaufenden Tuberkulose des lymphatischen Apparatus Ergebnis s d allg Path und path Anat 1903 XI Abt 9 502

7 REED D M On the pathological changes in Hodgkin s disease with special reference to its relation to tuberculosis Johns Hopkins Hosp Report 1902 X 133

8 ZIEGLER K Die Hodgkinsche Krankheit Jena 1911

9 SIMONDS J P Hodgkin s disease Arch Path and Lab Med 1926 I 304

10 WALLHAUSER A Hodgkin s disease Arch Path 1933 XVI 522 and 672

11 CHEVALLIER P and BERNARD S La maladie de Hodgkin s Masson et Cie Paris 1932

12 STERNBERG C Lymphogranulomatose und Reticuloendotheliose Ergebniss d allg Path und path Anat 1936 XXX 1

13 UDDSTRÖMER M On the occurrence of lymphogranulomatosis (Sternberg) in Sweden 1915–1931 and some considerations as to its relation to tuberculosis Acta Tuberculosa Scand 1943 Supp I pp 1–2 5

14 Caracteres anatomo — Chimques de la Granulomatose Maligne — Rapport — Congres Français de Med 22nd Session Paris 1932

15 JACKSON H JR and PARKER F JR Hodgkin s Disease New England Journal of Med 1944 CCXXX 1 CCXXXI 35 and 639 1945 CCXXXII 547 CCXXXIII 369 1946 CCXXXIV 3, and 103

16 YAMASAKI M Zur Kenntnis der Hodgkinschen Krankheit und ihres Überganges in Sarkom Zeitschrft f Heilkund 1904 XXV 269

17 FRAENKEL E und MUCH H Bermerkungen zu Aetiologie der Hodgkin chen Krankheit und der Leukaemie lymphatica Munch med Wochenschrft 1910 LVII 685

From all available evidence it must be concluded that irradiation and particularly the most recent methods of administering x ray are valuable forms of therapy in Hodgkin s disease It induces remissions controls very largely the swelling of lymph nodes thereby relieving pressure symptoms and undoubtedly prolongs the life of some patients Even though irradiation is not curative, it at least affords comfort to many patients who otherwise would undergo great suffering

BIBLIOGRAPHY

1 HODGKIN TH On some marked appearances of absorbent glands and spleen Trans Medico-Chirurg Soc London 1832 XVII 6°

2 ROLLESTON H D Some aspects of lymphadenoma (Hodgkin s disease) Practitioner 1911 I

3 FOX H Remarks on presentation of *microscopical preparations made from some of original tissue described by* Thomas Hodgkin 1832 Guy s Hosp Report, 1936 LXXXVI 11

4 WILKS S Cases of lardaceous disease and some allied affections with remark Guy s Hosp Report 1856 II 103

5 WILKS S Cases of enlargement of lymphatic glands and spleen (or Hodgkin s disease) Guy s Hosp Report 1865 XI 56

6 STERNBERG C Über eine Eigenartige unter dem Bilde der Pseudo leukami verlaufende *Tuberkulose der lymphatischen apparatus, Zeitschrift fur Heilkund* 1898 XIX 21

6(a) STERNBERG C Universelle Primarekrankungen des lymphatischen Apparatu Centralbl f d Grenzgebiet d Med und Chir 1899 II 641 711 770 813 and 847

6(b) STERNBERG C Primarekrankungen des lymphatischen und haematopoieti schen Apparatus Eigenartige under dem Bilde der Pseudo leukamie verlaufenden Tuberkulose des lymphatischen Apparatu Ergebnis d allg Path und path Anat 1903 XI Abt 9 50

7 REED D M On the pathological changes in Hodgkin s disease with special reference to its relation to tuberculosis Johns Hopkins Hosp Report 190 X 133

8 ZIEGLER K Die Hodgkin sche Krankheit Jena 1911

9 SIMONDS J P Hodgkin s disease Arch Path and Lab Med, 1926 I 394

10 WALLHAUSER A Hodgkin s disease Arch Path 1933 XVI 522 and 672

11 CHEVALLIER P and BERNARD S La maladie de Hodgkin s Mas on et Cie Paris 1932

12 STERNBERG C Lymphogranulomatose und Reticuloendotheliose Ergebniss d allg Path und path Anat 1936 XXX 1

13 UDDSTRÖMER M On the occurrence of lymphogranulomatosis (Sternberg) in Sweden 1915 1931 and some considerations as to its relation to tuberculosis Acta Tuberculos Scand 1943 S pp I pp 1-2

14 Caracteres anatomo — Cliniques de la Granulomatose Maligne — Rapports — Congres Français de Med 22nd Session Paris 1932

15 JACKSON H JR and PARKER F JR Hodgkin s Disease New England Journal of Med 1944 CCXXX 1 CCXXXI 35 and 639 1945 CCXXXII 54, CCXXXIII 369 1946 CCXXXIV 3, and 103

16 YAMASAKI M Zur Kenntnis der Hodgkinschen Krankheit und ihres Überganges in Sarkom Zeitschrift f Heilkund 1904 XXV 269

17 FRAENKEL E und MUCH H Bermerkungen zu Aetiologie der Hodgkinschen Krankheit und der Leukaemie lymphatica Munch med Wochenschrift 1910 LVII 685

17(a) FRAENKEL F Ueber die sogenannte Hodgkinsche Krankheit (Lymphomatosis granulomatosa) Deutsch med Wochenschrft 1912 XXXVIII 637
18 HIRSCHFELD H Ueber Pseudoleukaemie und ahnliche Krankheitszustande Berl klin Wochenschrft 1908 XLV 2227
18(a) HIRSCHFELD H Die Pseudoleukaemie Ergeb d inn Med u Kinderheilk 1911 VII 161
19 L ESPERANCE E S Experimental inoculation of chickens with Hodgkin s disease nodes Jour Immunol 1929 XVI 27 and 37
19(a) L ESPERANCE E S Study of a case of Hodgkin s disease in a child Jour Immunol 1930 XVIII 133
20 VAN ROOYEN C E Etiology of Hodgkin s disease with special reference to B tuberculosis avis Brit Med Jour 1933 I 50
21 LONGCOPE W T The pathological histology of Hodgkin s disease Bull Ayer Clin Lab Penn Hosp 1903 I 1
22 DENEGRI E and MILREMET C W Zur Etiologie des malignen Granuloms Centralbl f Bact 1913 LXVIII 292
23 BUNTING C H and YATES J L An etiological study of Hodgkin s disease, Jour Am Med Assoc 1913 LXI 1803 1914 LXII 516
23(a) GRUMBACH A Experimentelle Studien uber die Etiologie des Lymphogranuloms Frankft Zeitschrift f Path 1925 XXXI 530
24 PARSONS P B and POSTON M A The pathology of human brucellosis South Med Jour 1930 XXXII 7 Am Jour Path 1939 XV 634
24(a) WISE N G and POSTON M A The coexistence of brucella infection and Hodgkin s disease A clinical bacteriological and immunological study Jour Am Med Assoc 1940 CXV 1976
25 FORBUS W D and GUNTHER J U The pathogenicity of strains of brucella obtained from cases of Hodgkin s disease South Med Jour 1941, XXXIV 376
26 KOFOID C A Occurrence of *Amoeba dysenteriae* in the lesions of Hodgkin s disease Jour Am Med Assoc, 1922 LXXVIII 1604
27 GORDON M H A clinical concept of lymphadenoma or Hodgkin s disease Studies of the etiology Rose Research on Lymphadenoma London 1932
28 GORDON M H Hodgkin's disease A pathogenic agent in the glands and its application in diagnosis Brit Med Jour 1933 I 641 recent advances in the pathology and treatment of lymphadenoma Proceed Royal Soc Med London 1934 XXVII 1035
29 VAN ROOYEN C E The interpretation and significance of Gordon s test in the diagnosis of Hodgkin s disease Edinburgh Med Jour 1937 XLIV 455
30 TURNER J C JACKSON H JR and PARKER F JR The etiological relation of the eosinophile to the Gordon phenomenon in Hodgkin s disease Am Jour Med Sci 1938 CXCV 27
30(a) EDWARD D S I Observations on cellular basis of the Gordon test for lymphadenoma Lancet 1938 I 936
30(b) McNAUGHT J B The Gordon test for Hodgkin s disease Jour Am Med Assoc 1938 CXI, 1 80

31 GRAND C G Tissue culture studies of cytoplasmic inclusion bodies in lymph nodes of Hodgkin s disease Proceed Soc Exp Biol and Med 1944 LVI 29
32 KUCZYNSKI M H and HAUCK G Zur Pathogenese des Lymphogranuloms Zeitschft f klin Med 1923 XCIX 10
33 FORBUS W D and DAVIS C L A chronic granulomatous disease of swine with striking resemblance to Hodgkin s disease Am Jour Path 1946 XXII 35
34 TWORT C G Aetiology of lymphadenoma summary of 6 years researches Jour Path and Bact 1930 XXXIII 539
34 STEINER P E Etiology of Hodgkin s disease II Skin reactions to avian and human tuberculin Arch Int Med 1934 LIV 11
34(a) STEINER P E Hodgkin s disease Search for an infective agent and attempt at experimental reproduction Arch Path 1934 XVII 749
35 CUNNINGHAM W F and McALPIN K Experiments with Hodgkin s disease attempts to reproduce it in anthropoid and other monkeys Arch Int Med 1923 XXXII 353
36 STEWART M J Discussion on Hodgkin s disease in man and animals Proceed Royal Soc Med 1926 XIX 48
37 CHAPMAN E M Studies in Hodgkin s disease II Unsuccessful experiments to transmit Hodgkin s disease to dogs by intralymphatic injection Proceed Soc Exp Biol and Med 1936 XXXIII 572
38 LONGCOPE W T Notes on experimental inoculation of monkeys with glands from cases of Hodgkin s disease Bull Ayer Clin Lab Penna Hospital Phila 1907 IV 18
39 GOLDMAN L B Hodgkin s disease an analysis of 212 cases Jour Am Med Assoc 1940 CXIV 1611
39(a) GOLDMAN L B and VICTOR A W Hodgkin s disease Salient features based upon study of 319 cases New York State Jour Med 1945 XLV 1313
40 GREENFIELD W S Specimens illustrative of the pathology of lymphadenoma and leukocythemia Trans Path Soc London 1878 XXIX 272
40(a) POTTER E L Hodgkin s disease with especial reference to its differentiation from other diseases of lymph nodes Arch Path 1935 XIX 139
41 STEINER P E Hodgkin s disease The incidence distribution nature and possible significance of the lymphomatous lesions in the bone marrow a review with original data Arch Path 1943 XXXVI 62
42 WEBER F P A case of late Hodgkin s disease (lymphoma granulomatosum) with remarks on various cases presenting the clinical picture of splenic anemia (Banti s disease) Am Jour Med Sci 1911 CXLII 508
43 KRUMBHAAR E B Hodgkin s disease of bone marrow and spleen without apparent involvement of lymph nodes Am Jour Med Sci 1931 CLXXXII 764
44 FALCONER E H and LEONARD M E Hodgkin s disease of the lung Am Jour Med Sci 1936 CXCI 780
45 CHARR R and WASCOLONIS A Pulmonary lesions in Hodgkin s disease Jour Am Med Assoc 1941 CXVI 913
46 HARDIN R L Jr A case of Hodgkin s disease with massive collapse and cavitation of the lung Am Jour Med Sci 1939 CXCVII 92

46(a) LDSALL D L Hodgkin s disease with a milky non fatty pleural effusion New York Med Jour 1905 LXXXII 535
47 SHERMAN F D Gastrointestinal manifestations of lymphogranulomatosis (Hodgkin s disease) Arch Int Med 1938 LXI 60
48 SPERMAN M G and RUBENSTEIN H I Hodgkin s lymphogranuloma (rectal stricture) report of a case Ann Int Med 1942 XVII 349
49 GINSBURG, S Hodgkin s disease with predominant localization in the nervous system Arch Int Med 102, XXXIX 571
50 CONYBEARE E T Some features of Hodgkin s disease Guy s Hosp Rep London 1933 LXXXIII 53
51 HARRELL G T Hodgkin disease with invasion of pericardium and gallbladder Review of literature and report of case with autopsy, Arch Path 1939 XXVIII 58
5 WEBER F P and LEDINGHAM S C G Über einen Fall von Lymphadenoma (Hodgkinsche Krankheit) der Mediastinums verbunden mit hochgradigen hypertrophischen pulmonal Osteo arthropathie Deutsch Arch f klin Med 1909 XCVI 217
53 STEINER P E Malignant lymphogranulomatous (Hodgkin s disease) cirrhosis of the liver Arch Path 193, XIII 109
54 GINSBURG S Lymphosarcoma and Hodgkin s disease Clinical characteristics Ann Int Med 1936 X 337
55 SYMMERS D The clinical significance of the pathological changes in Hodgkin disease Am Jour Med Sci 1924 CLXVII 157 and 313
56 WINKELMAN N W and MOORE M T Hodgkin s disease of the nervous system Arch Neurol and Psych 1941 XLV 304
57 MELTON E I and McNAMARA W L Hodgkin s disease involving the pituitary with diabetes insipidus Ann Int Med 1946 XXV 525
58 GROSZ S Über eine bisher nicht beschriebener Hauterkrankung (Lymphogranuloma cutis) Beitrag z path Anat u z allgemein Path 1906 XXXIX 405
58(a) REIMANN H A HAVENS W P and HERBERT P A Hodgkin s disease with specific lesions occurring first in the skin Arch Int Med 194 LXX 434
59 BERSACK S R An unusual case of cutaneous Hodgkin s disease with terminal blood stream spread Jour Am Med Assoc 1944 CXXVI 1025
60 GALLOWAY J Hodgkin s disease Brit Med Jour 19 2 II 1201
61 MURCHISON C Case of lymphadenoma of lymphatic system spleen liver lung heart diaphragm dura mater etc Transact Path Soc London 1870 XXI 372
6 EBSTEIN W Das chronische Ruckfallsfieber eine neure Infectionskrankheit Berlin klin Wochenschrft 1887 XXIV 565 and 837
63 PEL P K Pseudoleukemia oder chronisches Ruckfallsfieber Berlin klin Wochenschrft 1887 XXIV 644
64 KUFFIN S Hodgkin s disease A study of a case with relapsing fever Am Jour Med Sci 1906 CXXXI 587
65 MacNALTY A S Lymphadenoma with relapsing fever Quart Jour Med 1911–1 V 58

66 WHITTINGTON T H Acute Hodgkin's disease with involvement of internal glands and relapsing pyrexia Quart Jour Med 1915-16 IX 83
67 TOWNSEND S R and BRAUNSTEIN A I Hyperchromic macrocytic anemia in association with Hodgkin's disease Canad Med Assoc Jour 1939 XLI 254
68 BUNTING C H The blood picture in Hodgkin's disease Johns Hopkins Hosp Bull 1914 XXV 80
69 BAYER S J Hodgkin's disease with leukopaenia Jour Am Med Assoc 1937 CVIII 876
70 MAJOR R H and LEGER L H Marked eosinophilia in Hodgkin's disease Jour Am Med Assoc 1939 CXII 2601
71 SEARS W G The blood in Hodgkin's disease with special reference to eosinophilia Guy's Hosp Rep 1923 LXXXII 40
72 STEWART S C Eosinophilic hyperleukocytosis in Hodgkin's disease with familial eosinophilic diathesis Arch Int Med 1929 XLIV 72
73 WISE B The sedimentation rate in Hodgkin's disease Jour Lab and Clin Med 1942 XXVII 1200
74 KOSTER L Changes in the sedimentation rate of erythrocytes in stored citrated blood Acta Med Scand 193 XCIII 420
75 FRIEDMAN B Maintenance of sedimentation rate of erythrocytes in vitro in cases of malignant tumors and Hodgkin's disease Am Jour Med Sci 1940 CC 810
76 KUSHNER J I Pregnancy complicating Hodgkin's disease (lymphogranuloma malignum) Am Jour Obst and Gyn 1941 XLII 536
77 KLAWANS O H Pregnancy complicated by Hodgkin's disease Am Jour Obst and Gyn 1942 XLIII 893
78 DESJARDINS A U and FORD F A Hodgkin's disease and lymphosarcoma a clinical and statistical study Jour Am Med Assoc 1923 LXXXI 925
79 GILMAN A and PHILLIPS F S The biological actions and therapeutic applications of the B chloroethylamines and sulfides Science 1946 CIII 409
80 GILMAN A Therapeutic action of chemical warfare agent Federation Proceedings 1946 V 285
81 RHOADS C P Nitrogen mustard in the treatment of neoplastic disease Official Statement Jour Am Med Assoc 1946 CXXXI 656
82 GOODMAN L S WINTROBE M M DAMASHEK W GOODMAN M J GILMAN A and McLENNAN M T Nitrogen mustard therapy Use of methyl Bis (beta chloroethyl) amine hydrochloride and tris (beta chloroethyl) amine hydrochloride for Hodgkin's disease lymphosarcoma leukemia and certain allied and miscellaneous disorders Jour Am Med Assoc 1946 CXXXII 126
83 JACOBSON L O SPURR C L BARRON E S G SMITH T LUSHBAUGH C and DICK G F Nitrogen mustard therapy Studies on the effect of methyl bis (beta chloroethyl) amine hydrochloride on neoplastic diseases and allied disorders of the hemopoietic system Jour Am Med Assoc 1946 CXXXII 263

84 YATES J L and BUNTING C H Results of treatment of Hodgkin s disease Jour Am Med Assoc 1917 LXVIII 747
85 SLAUGHTER D P and CRAVER L F Hodgkin s disease Five year survival note value of early surgical treatment, notes on 4 cases of long duration Am Jour Roentgenol 1942 XLVII 596
86 WALLHAUSER A and WHITEHEAD J M Immunological method in Hodgkin s disease a preliminary report Ann Surg 1928 V 29
87 UTZ L and KEATING L Hodgkin s disease a treatise Med Jour Australia 1931 I 307 II 41 1932 I 521
88 GASCOIN H Maladie de Hodgkin s traite par le venin de crapaud, Sang 1945 XI 565
89 BURNAM C F Hodgkin disease with special reference to its treatment by irradiation Jour Am Med Assoc 1926 LXXXVII 1445
90 GILBERT R Radiotherapy in Hodgkin s disease (malignant granulomatosis) Am Jour Roentgenol 1939 XLI 198
91 O BRIEN F W End results in irradiated Hodgkin s disease Am Jour Roentgenol 1941 XLVI 80
92 DESJARDINS A U Roentgen treatment for Hodgkin s disease and lymphosarcoma of chest Jour Am Coll Chest Physicians 1945 XI 3
92(a) DESJARDINS A U Salient features in the treatment of Hodgkin disease and lymphosarcoma with roentgen rays Am Jour Roentgenol and Radium Therapy 1945 LIV 707
93 ALEXANDER O Irradiation pneumonitis case Bull Johns Hopkins Hosp 1944 LXXV 109
94 REINHARD E H MOORE C V BIERBAUM O S and MOORE S Radioactive phosphorus as a therapeutic agent A review of the literature and analysis of the results of treatment of 155 patients with various blood dyscrasias lymphomas and other malignant neoplastic diseases Jour Lab and Clin Med 1946 XXXI 107
95 HAHN P F and SHEPPARD C W Selective radiation obtained by the intravenous administration of colloidal radioactive isotopes in diseases of the lymphoid system South Med Jour 1946 XXXIX 558

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CHAPTER 1 A

MYCOSIS FUNGOIDES LYMPHOBLASTOMA OF THE SKIN AND ALLIED CONDITIONS AS GENERAL DISEASES

By HAMILTON MONTGOMERY

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Introduction

Mycosis fungoides has been regarded as a cutaneous disease presenting a rather characteristic clinical appearance which will be described later Mycosis fungoides may involve only the skin or it occasionally may involve various internal organs[8, 88] It frequently terminates as one of the other lymphoblastomas namely leukemia (lymphatic myelogenous and monocytic) Hodgkin's disease or various types of lymphosarcoma[1, 37, 41, 61, 8, 83, 86, 2] Whereas mycosis fungoides is primarily a cutaneous disease many of the other lymphoblastomas may have a primary autochthonous cutaneous origin although cutaneous changes usually are secondary to metastasis or extension from within At times

multiple types of lymphoblastomas or allied conditions may occur simultaneously in the same case both on the skin and in various internal organs. I am in accord with the many authors who believe that there is a close relationship between the various lymphoblastomas[33, 61, 7, 108, 111, 114], but until more definite evidence is afforded concerning the neoplastic versus the benign inflammatory, infectious or virus origin or even a deficiency state of these diseases, it is important to distinguish between them whenever possible.

It is important to recognize the cutaneous manifestations, both the specific and nonspecific ones which have been reported as occurring in 10 to 40 per cent of various types of lymphoblastomas, as these cutaneous manifestations often predominate over any internal manifestations and offer valuable aid in diagnosis regarding systemic involvement on the one hand or distinction from a benign dermatosis on the other hand. One should correlate the dermatological and physical findings with the results of microscopic examination of specimens of skin[39, 66, 74], lymph nodes and sternal bone marrow with the results of hemocytological studies including the study of imprint or skin smears of material obtained for biopsy, with roentgenological studies and in certain instances with the results of other laboratory tests. Despite this correlation it often is impossible to make a definite diagnosis as to the type of lymphoblastoma, although the cutaneous pathological changes may be characteristic of lymphoblastoma but not specific as to type of lymphoblastoma. A prolonged period of observation and multiple examinations may be necessary at times before one can make the final diagnosis.

It is not pertinent to consider in this chapter the different hemocytological concepts regarding the origin of various forms of leukocytes[4, 13, 14]. For practical purposes they are stem or blast cells for lymphocytic, myelogenous and monocytic leukemia, disregarding the monovalent, dualistic and trivalent conceptions of various hemocytologists concerning the origin of leukocytes. If one follows the unitarian theory, the autochthonous cutaneous origin of even *myelogenous* leukemia and monocytic leukemia including reticulo endotheliosis can be readily explained. The hemocytological changes, the histopathological changes in the cutaneous lymph nodes and the pathological changes in the internal organs in cases of different types of lymphoblastomas are considered in other chapters.

This chapter is supplementary to the chapters on leukemia by Isaacs (Volume II, Chapter XVII), Hodgkin's disease by Longcope

(Volume IV, Chapter I), reticulum cell sarcoma (Volume IV, Chapter I D) and giant follicle lymphoma (follicular lymphoblastoma) and lymphosarcoma by Jackson and Parker (Volume IV, Chapter I E). Pertinent references to these conditions may be found in these chapters and will be repeated only in regard to cutaneous changes. The literature on the cutaneous manifestations has become so voluminous that I have selected when possible representative articles which in themselves contain references to the older[3, 84, 100] and more recent literature.[4, 6, 8, 113, 12] This chapter is also based on correlation of findings in more than 600 cases of cutaneous lymphoblastoma in which the patients were seen at the Mayo Clinic and in which one or more specimens of the cutaneous lesions were obtained for biopsy. Most of the specimens were obtained from specific lesions although in a third of the cases diagnosis as to type of lymphoblastoma could not be determined by histopathological examination. In another third of the cases the cutaneous changes were characteristic of mycosis fungoides. Of all the lymphoblastomas specific changes occurred least frequently in Hodgkin's disease. In a great many other cases of cutaneous lymphoblastoma in which the patients were observed in the Mayo Clinic Section on Dermatology by my associates and myself histopathological studies of the cutaneous lesions were not made for various reasons. In practically all of the cases there was a correlation between the hemocytological, roentgenological, systemic and other laboratory findings. It has been our good fortune to have observed a few cases, especially cases of mycosis fungoides, for as long as twenty or more years. The statistical analysis of the 600 cases of cutaneous lymphoblastoma will not be given at this time because necropsy was performed in very few of these cases either at the clinic or elsewhere. Observation of large numbers of cases of lymphoblastoma at various dermatological meetings during the past twenty-four years further supports the grouping of various types of this disease under the term lymphoblastoma.

Etiology Including Historical Consideration

Mycosis fungoides was first described by Alibert in 1806 as "pian fongoide" because of its resemblance to yaws, but in 1832 he called the condition "mycosis fungoides" because of the presence of mushroom-like tumors.[3] Auspitz in 1885 suggested the term "granuloma fungoides" which still is employed by physicians who regard this disease as an in-

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This chapter is supplementary to the chapters on leukemia by Isaacs (Volume II Chapter XVII) Hodgkin's disease by Longcope

which he designated as "myeloblastoma." Mallory included Hodgkin's disease with lymphoblastoma, whereas the tendency today would be to group it with reticulo-endotheliosis or with reticulum cell type of sarcoma. Symmers[108] at first regarded mycosis fungoides as a cutaneous manifestation of a systemic disease of toxic origin but later associated the condition with Hodgkin's disease and other lymphoblastomas and denied that mycosis fungoides was a disease entity. Because of the tendency of mycosis fungoides to terminate as one of the other lymphoblastomas there has been a tendency for some dermatologists and some pathologists to say that the disease from the beginning is a reticulo-endotheliosis, a monocytic leukemia, a form of Hodgkin's disease or even a form of reticulum cell sarcoma. However, cases in which the disease has been associated with lymphatic leukemia have been encountered also. Some authors, while still regarding mycosis fungoides as of an inflammatory nature, would separate the erythrodermic and especially the d'emblée forms as being of neoplastic nature. The French tend to group mycosis fungoides with disturbances of the hematopoietic system[32, 8] under the heading of "hematodermies."

The term "lymphoblastoma" has been criticized by some internists and pathologists who regard the conditions included under this term as *inflammatory* and by others who would limit the term to denote conditions strictly of lymphocytic origin. Thus this group of diseases is *discussed in the literature under various terms such as* "lymphoma," "lymphocytoma," "leukosis" and "reticulosis," with or without the use of such prefixes as benign or *malignant*[14, 37, 38, 43, 4, 9, 110, 117, 118] I have adhered to the term "lymphoblastoma" and other terms used in other chapters in *Oxford Medicine* which I realize are not in conformity with the terms recommended by the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood forming Organs[18]. I am aware that further reports are to be issued from this Committee and believe it preferable, for the most part, to use older terminology until the new classification of terminology is completed.

The prolonged duration of mycosis fungoides of from five to twenty and even forty years in some cases would seem to deny a malignant origin for this disease, as would reported cases in which there was no evidence of involvement of internal organs at the time of necropsy. The same is true of cases in which involvement of lymph nodes and internal organs is proved pathologically to be merely inflammatory in character or to simulate the histological changes of mycosis fungoides without

flammatory or infectious granuloma The term, "mycosis fungoides", however has persisted despite the fact that the condition has nothing to do with mycosis or other fungus diseases This is comparable to the perseverance of the terms "sarcoid" and "sarcoidosis", which have nothing to do with sarcomas Thus the cutaneous lesions of mycosis fungoides were described by Alibert twenty six years before Hodgkin described the condition which bears his name, and thirty-nine years before Bennett and Virchow independently described leukemia

Among early dermatologists who sought the cause of mycosis fungoides Gillot in 1869 who based his opinion on the research of Bazin and on the histological studies of Ranvier concluded that mycosis fungoides was due to development of reticular lymphoid tissue in the skin, and that there was a cutaneous manifestation of lymphoid diathesis He therefore proposed the name "lymphadenee cutanee" Port in 1864 spoke of a sarcomatous origin, and subsequent writers were divided regarding the benign inflammatory or infectious granulomatous character as compared with the neoplastic character of the disorder, and finally on whether or not an inflammatory process eventually became neoplastic The literature contains reports of cases in which mycosis fungoides was associated with pseudoleukemia, Hodgkin's disease and lymphosarcoma Kaposi in 1885 and in later articles[59] regarded mycosis fungoides as a form of sarcomatosis grafted on a previous dermatosis a view concurred in by Brocq who included parapsoriasis among the previous dermatoses Paltauf first regarded mycosis fungoides as a lymphosarcoma and later as an infectious granuloma Many authors searched unsuccessfully for causative organisms Most dermatologists during the first two decades of this century regarded mycosis fungoides as an inflammatory infectious granuloma and believed that the occasional association of leukemic or sarcomatous change was merely an incidental finding

Among dermatologists Fraser in 1917, 1925[33, 34] and later[35] emphasized the relationship of mycosis fungoides to lymphosarcoma and also to leukemia, as did Keim[60] in 1924 Wile and Stiles[110] and later, many other dermatologists

Among the pathologists Warthin[111] in Osler's "System of Medicine" in 1908 used the term "lymphocytoma" to describe the various lymphoblastomas The latter term was created by Mallory in 1914 He used this term to designate the same pathological conditions that are classified under this term at present, with the exception of myelogenous leukemia

involution of one or more lesions or complete remission of the disease over a period of months and occasionally years

It becomes apparent that as yet there is no uniform agreement as to the nosologic position of mycosis fungoides in relation to the other lymphoblastomas or in regard to its benign inflammatory or neoplastic character Our knowledge of the cause of the disease has advanced little over what was known regarding it during the last half of the past century The etiological concepts of the various types of leukemia Hodgkin s disease and lymphosarcoma are considered in the respective chapters on these diseases

Cutaneous Changes in General

The cutaneous changes may be specific as to type (mycosis fungoides) or nonspecific or toxic (Hodgkin s disease) Cutaneous manifestations especially those formerly grouped as nonspecific will be described before the cutaneous symptoms and pathological changes in different types of lymphoblastoma are considered

Pruritus — Generalized or localized pruritus with or without excoriation and lichenification is a prodromal or concomitant symptom especially of Hodgkin s disease and mycosis fungoides It is the usual accompaniment of exfoliative dermatitis or erythroderma whether or not of lymphoblastomatous origin Generalized pruritus may be associated with various other systemic diseases such as hyperthyroidism and hypothyroidism nephritis arteriosclerosis with and without senile skin changes prostatitis diseases of the liver and gallbladder even without jaundice malignant diseases of the abdomen lymphoblastoma diabetes mellitus the ingestion of various drugs and finally it may be the result of functional and organic nervous diseases Generalized pruritus caused by *Sarcoptes scabiei*, pediculi and other animal parasites or by xerosis (asteatosis) associated with too frequent bathing can be excluded readily by the concomitant findings There often has been a tendency among dermatologists and other physicians to make a diagnosis of neurotic excoriations or senile pruritus in cases in which a more careful study would reveal the systemic often lymphoblastomatous nature of the pruritus

Urticaria and Erythema Multiforme — These lesions occur in any stage of lymphoblastoma They are usually transitory but when chronic

pathological evidence of any malignant change In my experience, however, in the majority of the cases, in which mycosis fungoides has been present for a long time the disease usually eventuates in one of the other types of lymphoblastoma including Hodgkin's disease and reticulum cell sarcoma There is an increase in reticulum cells and monocytes of different types in both mycosis fungoides and monocytic leukemia including reticulo endotheliosis and various stages of Hodgkin's disease It is understandable therefore why a sharp dividing line cannot be drawn between these conditions in all cases Winer said that the reticulum cells in mycosis fungoides may differentiate in two diverse types and undergo liquefaction necrosis or become malignant The d emblee or rapidly growing tumor forms of mycosis fungoides may from the beginning be Hodgkin's disease or other forms of lymphoblastoma

That there is a definite relation to the reticulo-endothelial system using the term in the broadest sense is revealed by an increase in the reticulum or lattice fibers in the cutaneous lesions of mycosis fungoides Hodgkin's disease, myelogenous and monocytic leukemia and reticulum-cell sarcoma There is little if any increase in these fibers in cases of lymphatic leukemia and so-called small round cell lymphosarcoma

It is my belief that in many cases of lymphoblastoma of the skin especially in cases in which the disease is of primary cutaneous autochthonous origin including cases of mycosis fungoides Hodgkin's disease and lymphocytoma the disease may start as a benign inflammatory process and as the result of repeated chronic inflammation irritation and trauma may eventuate only after a period of months or years in a true malignant disease whether of leukemic or sarcomatous origin This is comparable to the benign inflammatory changes which are seen in the earliest stages of Kaposi's sarcoma and which eventuate in malignant sarcoma A similar phenomenon is seen in the transitions of benign epithelial neoplasms and precancerous dermatoses into malignant epitheliomas only after a period of years[78, 79] Many authors would regard this concept as retrograde or a step backward yet experimental work especially that of Fischer-Wasels demonstrates that it is possible for a benign or infectious process to become neoplastic In experimental epithelioma (carcinoma) in animals up to a certain point, even when histological examination discloses evidence of malignant change, the process may be a reversible one and the lesions may undergo involution after removal of the carcinogenic agent Such a phenomenon probably takes place in cases of mycosis fungoides in which there is spontaneous

type of lymphoblastoma or may develop later in the course of the disease No part of the skin is free from involvement In as many as 50 per cent of all cases in which exfoliative dermatitis occurs in the later decades of life the disease may be of lymphoblastomatous origin Distinction from exfoliative dermatitis due to various benign dermatoses usually can be made by histopathological study

Lymphadenopathy — Enlargement of the lymph nodes may be very prominent in cases of exfoliative dermatitis or generalized erythroderma no matter what the cause and also in cases of localized involvement by various types of dermatitis As a rule biopsy reveals simply an inflammatory reaction Distinction regarding the tenseness fluctuation or attachment of the lymph nodes to the skin or to the underlying structures is not of diagnostic value Pautrier and Woringer in 193 and 1937 referred to enlargement of the lymph nodes in exfoliative erythroderma as a lipo melanique reticulosis (reticulose lipo melanique) and said that melanin pigment was transferred from the epidermis through the lymphatics to the lymph nodes[37] They associated this process in some cases with lymphoblastoma but I have seen this phenomenon in association with many inflammatory dermatoses with or without increased pigmentation of the skin

Pigmentation of the Skin — This may occur with any of the lymphoblastomas and may not be related to the administration of arsenic or other drugs to internal involvement of the chromaffin system or to specific cutaneous involvement It should be distinguished from pigmentation secondary to pruritus and various dermatoses such as lichen planus dermatitis herpetiformis and drug eruptions as well as from various diseases such as Addison s disease which involve the chromaffin system Pigmentation that is a sequel of roentgen therapy is readily recognized by angular linear delineation of the lesions which are limited to the areas exposed to the roentgen rays

Elephantiasis (Lymphedema) — Elephantiasis of part of the face genitalia or one or more extremities may result from involvement of adjacent lymph nodes by a lymphoblastomatous process occasionally it may result from extension of a lymphoblastomatous infiltrate into the involved lymph vessels Lymphedema of the face with or without nodular infiltration may result in a leonine expression Priapism is encountered occasionally There may be an associated lymphadenopathy

Alopecia and Dystrophic Changes in the Nails — These are not an infrequent occurrence in some of the cases of lymphoblastoma but usu

and persistent, they may represent a toxic manifestation and may be specific in character. One must distinguish these lesions from those caused by allergic phenomena, including drug eruptions and toxic reactions which are the result of treatment.

Bullous and Pemphigoid Lesions. — These lesions are seen occasionally in cases of lymphoblastoma. They are independent of any medication and usually occur in association with acute or fulminating and terminal manifestations of any one of the lymphoblastomas and they may be either specific or nonspecific in type.

Purpuric and Hemorrhagic Lesions. — These lesions are encountered most frequently in acute forms of leukemia and in the terminal stages of any of the lymphoblastomas. Purpuric and hemorrhagic lesions may predominate and be specific in type even in the earliest stages of monocytic leukemia (Schilling) including reticulo-endotheliosis.

Herpes. — Herpes zoster, either localized or at times generalized, and occasionally, herpes simplex occur especially in lymphatic leukemia and Hodgkin's disease.[6, 98, 119] *A persistent and severe herpes zoster* developing in the later decades of life frequently is indicative of lymphoblastoma or other malignant lesions of the internal organs. Specific lymphoblastomatous infiltrations in the skin or involving nerve roots *occur occasionally and have been observed in all types of lymphoblastoma* except mycosis fungoides.

Eczematoid and Psoriasiform Lesions. — All variations from ill-defined superficial, noninfiltrated, erythematous, scaly plaques to discrete *and confluent papular and vesiculopustular eruptions, often of* eczematoid character and either localized or generalized, may be a prodromal symptom of any of the lymphoblastomas, especially mycosis fungoides. These lesions must be distinguished from contact or atopic *dermatitis (eczema), from drug and other* toxic eruptions and from so called infectious eczematoid dermatitis by the concomitant findings including histopathological examination which may reveal early histopathological evidence of mycosis fungoides. The same is true in regard *to the distinction of* psoriasiform and *parapsoriasiform lesions of pre*mycotic mycosis fungoides from the lesions of true psoriasis.

Ulcers and Nodules. — Discrete or multiple ulcers or nodules occur in different types of lymphoblastoma. They usually represent a specific infiltration but are not clinically characteristic.

Exfoliative Dermatitis and Generalized Erythroderma. — These lesions may be a prodromal, specific or nonspecific manifestation of any

It is much greater than the period of survival in cases of other types of lymphoblastoma

The cutaneous appearance of the lesions of mycosis fungoides may not be diagnostic and this is especially true in the early stages of the disease Even in the infiltrative or well developed lesions what may appear clinically to be mycosis fungoides may prove histopathologically or by other studies to be one of the lymphoblastomas The most characteristic changes clinically are seen in the infiltrative stage of the disease

Pruritus may be a prodromal symptom for many years before cutaneous infiltrations appear It is customary to divide the disease into the following stages (1) the eczematoid or premycotic stage (2) the infiltrative stage and (3) the tumor stage In addition there is the so called generalized erythrodermic or exfoliative type of Hallopeau-Besnier which may represent either a beginning phase or an end stage of the disorder and finally there is the so-called mycosis fungoides d emblee or the Vidal Brocq type in which the condition begins as multiple tumors and usually runs a rapid course Spontaneous involution may occur without treatment in any of the various stages or types of mycosis fungoides although it rarely does so in the tumor stage but the lesions recur after a period of months or years Involvement of the mucous membranes is uncommon[6] Various degrees of alopecia may result especially from infiltrated plaques in the scalp Verrucous lesions[58] and generalized bullous lesions simulating pemphigus have been observed[40, 44] especially in the terminal stage of the disease Bullous lesions have been attributed erroneously to the administration of iodides[27] in cases of mycosis fungoides in which the patients have died and in other cases these lesions have been misinterpreted as multiple malignant epithelial proliferations of epidermal structures[63] Dependent on the stage extent and activity of the disease there may be varying degrees of enlargement of adjacent lymph nodes but histopathological examination usually discloses that the enlargement is nonspecific The case reported by Ormsby Finnerud and Apfelbach is an example of the relatively uncommon involvement of lymph nodes and internal organs without transition of the disease to other types of lymphoblastoma

In the eczematoid or premycotic stage there may be superficial non infiltrated psoriasiform plaques which are suggestive of the dermatological condition known as parapsoriasis en plaque Histopathological examination of these plaques reveals the early changes of mycosis fungoides Dostrovsky and Sagher reported a case in which poikilo

ally are seen in association with cutaneous changes These changes usually are nonspecific in character

Lesions of the Mucous Membranes[72] —These lesions are seen especially in acute forms of lymphoblastoma, particularly in the various types of acute leukemia The lesions may be nonspecific or specific in type, they may be ulcerated bullous hemorrhagic or even necrotic in character and must be distinguished from lesions of pemphigus thrush stomatitis and various granulomatous processes including tuberculosis syphilis, moniliasis deep seated fungous infections such as blastomycosis and also from other neoplastic processes The external auditory canal and the tympanum may be the site of hemorrhagic blebs and this involvement may be associated with otitis media and with hemorrhages in the middle or inner ear with or without conductive deafness and the sudden onset of Meniere s syndrome Involvement of the nose is manifested by epistaxis or true leukemic infiltration The gums are hypertrophic, bleed easily and may be the site of secondary infection due to Vincent's organisms Gingivitis may be a primary specific symptom of monocytic leukemia or may be secondary to agranulocytosis Involvement of the mucous membranes of the genitalia is seen also

Mycosis Fungoides (Granuloma Fungoides)

Mycosis fungoides usually begins in adult life especially in the latter decades although it has been known to affect children six years of age The literature contains reports of very few cases in which the patients had not reached the age of puberty A review of all cases of mycosis fungoides in which the patients were observed at the Mayo Clinic in a recent period of eleven years has failed to disclose a single case in which the disease affected a child Mycosis fungoides is more frequent among men than among women It was regarded formerly to be relatively rare in negroes but several cases in which the disease affected negroes recently have been reported[103] Azulay (personal communication) found that, in three out of nine cases of mycosis fungoides observed in Rio de Janeiro the patients were negroes Apparently no race is immune Death occurs in from six months to forty or more years after the onset of the disease In cases in which the patients are not treated the average period of survival is about five years after the onset of the disease but this period is considerably longer in cases in which treatment is employed

patches of dermatitis or cutaneous plaques which simulate eczema, psoriasis, lichen planus and neurodermatitis.

In the infiltrative stage the disease assumes its more characteristic appearance. This consists of multiplicity of types of lesions which vary from superficial scaling plaques to urticarial, erythema multiforme-like lesions and infiltrated plaques and nodules. There is a tendency for the various lesions to merge in an arciform arrangement. The multiplicity of types and stages of lesions present at the same time together with the arciform pattern of the cutaneous eruption permits a definite diagnosis to be made. In the third or tumor stage nodules and tumors of varying sizes with or without ulcers, including large fungating ulcerative masses involving the side of the face, scalp, back or extremities, become manifest. Some of the tumors and masses are pedunculated, oval or lobulated, and vary in color from bluish to brownish red. Involvement of the face may present a leontiasic change simulating that seen in leprosy.

The duration of the disease in any one stage varies greatly[113] and there may be merging of the different stages of the disease. The tumor stage often begins within a few months after the onset of the infiltrative stage. As stated previously, the so-called mycosis fungoides d'emblee runs a relatively rapid course and may from the beginning histologically represent Hodgkin's disease or one of the other types of lymphoblastoma. Pruritus is more likely to be absent in the d'emblee form but occasionally may be absent throughout the course of mycosis fungoides, as it was in a case in which the patient was a physician aged fifty-three years who had had premycotic and infiltrative lesions of mycosis fungoides for eighteen years but did not have pruritus at any time. Transitions of mycosis fungoides to any of the other types of lymphoblastoma are illustrated in figures 1 to 5 and by the case reports.

Pathology. — The histopathological changes of mycosis fungoides in the earliest premycotic or eczematoid stage may resemble those of various benign dermatoses. If a specimen of a lesion that has been present for some length of time is removed for biopsy, diagnostic changes may be seen in the infiltrate in the cutis[33] This infiltrate is composed of different types of cells, including lymphocytes, polymorphonuclear leukocytes, eosinophils, plasma cells, endothelial cells, monocytes (including histiocytes) and connective tissue cells of different types. Pyknosis and karyorrhexis of the individual cells are present, and there is a tendency for endothelial cells to be arranged in clumps or for reticulum cells to form pseudogiant cells (Figs. 4a and 5a and *b*). Sometimes microscopic

derma was the only manifestation of the initial stage of mycosis fungoides More frequently poikiloderma-like changes occur later in

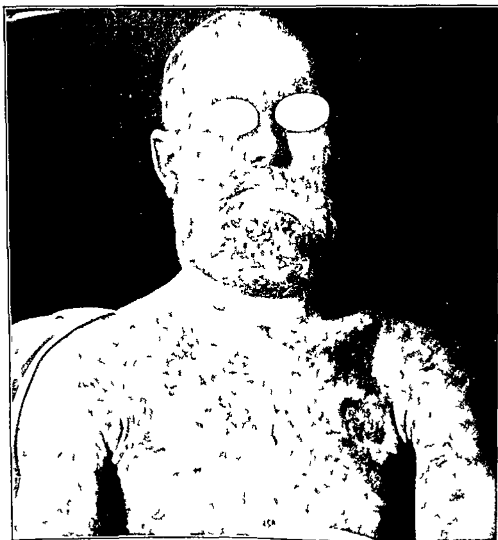


Fig 1 Typical clinical picture of mycosis fungoides with multiplicity of types of lesions The cervical adenopathy suggested Hodgkins disease A specimen of skin revealed mycosis fungoides and specimens of lymph nodes revealed lymphosarcoma Hemocytological findings were those of lymphatic leukemia

the disease and are related to spontaneous remission or follow roentgen therapy whether or not they are the result of such therapy Other types of lesions which occur in the premycotic stage include ill defined

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Fig. Generalized exfoliative dermatitis of four years duration Patient was a man aged 59 years The generalized enlargement of the lymph nodes probably was inflammatory in origin An enlarged lymph node was not examined microscopically Cutaneous biopsy disclosed mycosis fungoides Hemocytological and roentgenological examinations did not disclose any abnormality Several courses of roentgen therapy produced temporary improvement but the patient died

examination of more than one specimen is necessary for diagnosis and many sections may have to be cut before these changes can be demonstrated It is important not to evaluate these changes on the basis of the



Fig 3 Poikiloderma like plaque of three years duration on the left buttock of a man aged 48 years Superficial parapsoriasiform plaques and nodulo ulcerative lesions of one year s duration on the right buttock Biopsy disclosed mycosis fungoides in one portion of this lesion and reticulum cell lymphosarcoma in another portion Roentgenological and hemocytological examinations did not reveal any abnormality Intensive roentgen therapy resulted in complete involution of all of the cutaneous lesions except those which had undergone ulceration Secondary anemia developed and the patient died at home (This illustration originally appeared as figure on page 185 of the following article Montgomery H and O Leary P A Micosis fungoide y linfoblastomas de la piel Rev Argentina de Dermatosif 23 181 199 1939)

infiltrate adjacent to an area of ulceration or excoriation as distortion in shape and size of the cells occurs in these areas in cases of many other pathological conditions Clumping of endothelial cells at the tips of



Fig Generalized exfoliative dermatitis of four years duration Patient was a man aged 39 years The generalized enlargement of the lymph nodes probably was inflammatory in origin An enlarged lymph node was not examined microscopically Cutaneous biopsy disclosed mycosis fungoides Hemocytological and roentgenological examinations did not disclose any abnormality Several courses of roentgen therapy produced temporary improvement but the patient died

capillary loops in the upper part of the cutis is seen in neurodermatitis and has been confused with the pseudoclumping of cells in mycosis fungoides and with Reed Sternberg cells (Figs 5*d* and *e*)

In the infiltrative stage there is thickening of the prickle cell layer which often is accompanied by formation of micro abscesses (Fig 4*b*) that are filled with lymphocytic and other monocytic cells in contradistinction to the polymorphonuclear leukocytes which occur in the microabscesses of psoriasis The infiltrate in the cutis varies greatly in density and extent Liquefaction degeneration of the basal cell layer and massive invasion of the epidermis by the cells in the infiltrate have resulted in an erroneous diagnosis of multiple malignant epithelial neoplasms In the tumor stage of mycosis fungoides the infiltrate tends to become more uniform in character and is composed chiefly of lymphocytes or at times of monocytic cells with or without an increase in the number of eosinophils A very marked eosinophilia may be present but unless mycosis fungoides is undergoing transition to Hodgkin s disease Reed Sternberg cells cannot be demonstrated In the tumor stage numerous mitotic figures frequently occur and the histological picture may merge with that of small cell lymphosarcoma on the one hand or reticulum cell lymphosarcoma on the other (Fig 5*c*)

The mycosis cell which is essentially a palely staining reticular or reticulum cell or large histiocyte has been described as being characteristic of mycosis fungoids[109] This type of cell and variations thereof however are found in other types of lymphoblastoma as well as in various inflammatory diseases involving the reticulo-endothelial system and in my opinion are without diagnostic significance In the infiltrative and tumor stages of mycosis fungoides frequently there is an increase in reticular or monocytic cells with longitudinal grooving of the nuclei of the cells so that on histopathological grounds alone one cannot be sure whether one is still dealing with mycosis fungoides or whether transition has occurred to monocytic leukemia especially of the Schilling type or reticulo endotheliosis In all stages of mycosis fungoides there is definite increase of reticulum fibers (Gitterfasern or lattice fibers) therefore this is not of value in distinguishing mycosis fungoides from monocytic leukemia

The hemocytological changes in mycosis fungoides are usually within normal limits except at times, for the presence of a moderate increase in the number of monocytes in the blood The monocytes however are well formed and are mature



Fig 4 *a* Very early premycotic stage of mycosis fungoides The patient also had multiple tumors but necropsy did not reveal any involvement of the internal organs The histopathologic changes simulate parapsoriasis en plaque yet the clumping of cells and other changes are similar to those shown in figure 5*a* (x100)

b Typical mycosis fungoides infiltrative stage Mocro abscess at x and polymorphous infiltrate limited chiefly to upper part of cutis (Hematoxylin and eosin stain x75)

c Chronic lymphatic leukemia Note lack of involvement of epidermis and dense infiltration situated throughout the cutis and pushing aside strands of connective tissue At this magnification the section is equally representative of all types of leukemia and most types of Hodgkin's disease and lymphosarcoma (x45)

d Tumor stage of mycosis fungoides undergoing transformation to reticulum-cell sarcoma Section obtained from the patient shown in Fig 3 Note the vascularity and the increase in the reticulum or lattice fibers stained black (Maersch Bielschowsky stain x52)

Skin Smears — Skin smears namely imprint and smears of specimens that have been cut in two have proved of great diagnostic value not only in mycosis fungoides but in other lymphoblastomas This procedure which has been employed by others in the past[8, 9, 106] has been described in detail by Wilson It is important that the specimen be cut in half with a clean dry knife that then the cut surface of the specimen be imprinted and smeared on slides just as smears from the peripheral blood are made and the smear be stained with Wright s or Giemsa s stain Winer in one case of mycosis fungoides demonstrated a malignant reticulum cell from an imprint of a cutaneous tumor In one case typical of mycosis fungoides which Wilson studied clinically and histopathologically many stem or blast cells were revealed in skin smears the cells however were too undifferentiated for further classification Repeated studies of the peripheral blood in this case gave negative results The patient died of the disease without evidence at postmortem examination of involvement of the internal organs and with negative studies of sternal marrow In another case Wilson and the hemocytologist at the Mayo Clinic were able to demonstrate stem or blast cells in the skin smear in a case of clinical mycosis fungoides but the stem cells were the type that fitted in distinctly with a diagnosis of monocytic leukemia or reticulo endotheliosis Smears of the peripheral blood were negative for any leukemia at the time of first examination but later smears of the peripheral blood were diagnostic and the patient died of monocytic leukemia At other times however skin smears simply confirmed the findings from the usual hemocytologic procedures In the past I have often been able to say on the basis of skin biopsy that a patient had lymphoblastoma but could not specify the type of lymphoblastoma because fixation in formalin and imbedding in paraffin result in shrinkage of cells and loss of the finer cytoplasmic and nuclear detail Skin smear from a specimen for biopsy on the other hand gives us clear cellular details as those seen in ordinary blood smears

Report of Cases — In order to illustrate various features of this disease several cases will be reported briefly

Case 1 — A medical student aged twenty six years first came to the clinic in 19 6 because of multiple plaques nodules and a vesiculopustular eruption which had been present on the trunk and extremities for ten years A diagnosis of premycotic stage of mycosis fungoides was confirmed by cutaneous biopsy and a diagnosis of mycosis fungoides was confirmed by subsequent biopsies throughout the course of the disease Dr O Leary and



Fig 5 *a* Mycosis fungoides early superficial plaque similar to the lesion shown in figure 4*a* There is a small amount of perivascular infiltrate but pyknosis karyorrhexis and clumping of cells are evident (x430)

b Similar changes in the tumor stage in another case of mycosis fungoides (x350)

c Tumor state of mycosis fungoides probably undergoing transition to reticulum cell sarcoma Note mitosis at x capillary lined with abnormal cells large reticular or reticulum cells yet pyknosis karyorrhexis and clumping of cells seen in mycosis fungoides (x575)

d Typical mononuclear and multinuclear cells of Hodgkins disease (x675)

e Pseudoclumping of endothelial cells of capillary loops in xerodermatitis (x675)

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I saw the patient on frequent occasions in a period of more than twenty years as did his family physicians The patient was very co operative regarding treatment There were exacerbations and remissions of the condition which at first responded to roentgen therapy but later became radioresistant Extensive exfoliative erythroderma and infiltrated and hemorrhagic lesions developed and were suggestive of leukemia He received a course of fever therapy and chaulmestrol (ethyl chaulmoograte) in 1938 This resulted in marked improvement and subsequent response to further roentgen therapy Up to 1945 he had received a total of about 700 roentgen treatments with both superficial unfiltered rays and intensive application of filtered irradiation to the spleen and other organs The total dose applied to any one cutaneous lesion or to any organ is not known but in some instances it exceeded many thousand roentgens The total dose was in excess of that reported by Levin and Behrman In 1942 symptoms of gastrointestinal obstruction developed and on two occasions laparotomy disclosed only benign scarring about the ileum and jejunum

When the patient was last seen at the clinic in 1945 he had multiple cutaneous ulcers generalized pigmentation and telangiectasia The telangiectasia probably was attributable in part to the intensive roentgen therapy A variable degree of enlargement of the lymph nodes had been present since 1937 There was prompt response of the cutaneous lesions to roentgen therapy in 1945, which suggested to Dr O Leary that a transition to lymphosarcoma had occurred Examination throughout the course of the disease including hemocytological and roentgenographical examination failed to reveal any other lymphoblastoma or evidence of systemic involvement

The patient continued his medical practice until June 1946 His physical condition gradually failed Severe anemia developed and repeated transfusions of blood were necessary The patient died of terminal pneumonia in September 1946 Necropsy performed at home revealed infiltrates in the skin esophagus intestines kidney heart pancreas lung and sternal marrow The infiltrates contained cells which resembled reticulocytes or lymphocytes and which were interpreted as consistent with the diagnosis of mycosis fungoides with secondary changes due to extensive roentgen therapy Dr A H Baggenstoss recently reviewed some of the slides which were available He emphasized the presence of abnormal cells which resembled lymphoblasts and monocytes and he noted the presence of numerous large cells which had indented nuclei and were suggestive of monocytic leukemia The number of monocytes present in the sections of skin at the time of necropsy was no greater than one would expect in a case of mycosis fungoides and for the most part the infiltration in the various organs was minimal and apparently secondary rather than primary

In this case the disease might be interpreted as mycosis fungoides which terminated as such or mycosis fungoides which terminated as aleukemic

reticulo endotheliosis or monocytic leukemia It is difficult to evaluate how much the intensive roentgen therapy influenced the blood picture as a whole The patient probably would not have lived thirty years after the onset of the disease if he had not received intensive treatment of different types

Case 2 — A woman aged forty three years came to the clinic because of premycotic and infiltrative stages of mycosis fungoides with plaques which involved most of the body and had been present for five years The diagnosis was confirmed by microscopic examination of specimens of the cutaneous lesions The results of general examination and various laboratory tests were essentially normal The lesions at first responded to superficial roentgen therapy but later they became resistant The patient received twelve treatments in the fever cabinet and responded temporarily to three courses of filtered roentgen irradiation applied to the splenic region A course of chaulmestrol at first produced partial and later produced complete involution of the lesion She was free of the disease four or five years but it eventually recurred and the patient died fifteen years after the onset of the disease Necropsy was not performed

Case 3 — A man aged thirty six years came to the clinic in 1934 because of mycosis fungoides which had been present for four years The diagnosis was confirmed by histopathological examination He was under repeated observation until his death which occurred twelve years later Response to treatment of different types was similar to that which occurred in cases 1 and and repeated hemocytological and roentgenographical examinations did not disclose any abnormality The fourth cutaneous specimen for biopsy which was obtained in August 1945 was the first to show areas of necrosis and a few eosinophils and atypical Reed Sternberg cells In addition there was evidence of roentgen dermatitis Shortly before death large necrotic ulcers developed and it was necessary to amputate the right leg at the thigh The patient died of congestive heart failure and terminal hemolytic streptococcic septicemia Necropsy performed at home revealed nodules in the lung and gastrointestinal tract These nodules contained a pleomorphic infiltrate This infiltrate contained many mononucleated giant cells and an occasional multinucleated giant cell which were suggestive of Hodgkin s disease The visceral lesions were not considered primary because of the minimal destruction of the organ involved

In this case the disease might be classified as mycosis fungoides which terminated as Hodgkin s disease although death was secondary to general debility caused by the cutaneous lesions

Case 4 — A man aged forty seven years came to the clinic in March 1947 because of an eruption which started ten months previously as dermatitis of the ankles but gradually spread and became generalized and exfoliative Examination disclosed marked enlargement of the inguinal lymph nodes and fungating lesions about the perianal region A clinical diagnosis of

mycosis fungoides was confirmed by histopathological examination. No evidence of any other type of lymphoblastoma could be demonstrated. Nitrogen mustard was administered but severe leukopenia developed and the patient died twenty six days after he came to the clinic. Necropsy revealed reticulum cell sarcoma of many of the internal organs.

Additional Cases. Goeckerman and I reported a case in which mycosis fungoides ran a rapidly fulminating course and terminated in cutaneous changes which I now would classify as reticulum cell lymphocytoma although no changes could be found in any of the internal organs at necropsy. Cases in which transitions occurred between mycosis fungoides and monocytic leukemia of both the Naegeli and Schilling types have been reported by Watkins and me. In one case in which a diagnosis of mycosis fungoides was made on the basis of clinical and histopathological findings at the clinic the patient died elsewhere and the case was reported by Berman as a case of leukemic reticulo endotheliosis in which the internal organs also were involved in the same pathological process.

Hodgkin's Disease

Hodgkin's disease[6] may begin at any time in life and is twice as prevalent among men as among women. Whereas Hodgkin's disease may have a primary autochthonous cutaneous origin, this is a very uncommon occurrence. Nonspecific toxic changes occur in 25 to 53 per cent of the cases[16, 48, 101]. Specific changes occur only occasionally. The division of Hodgkin's disease into paragranulomatous, granulomatous and sarcomatous forms on the basis of pathological findings as described by Jackson and Parker or the earlier classification of Callender who divided Hodgkin's disease into benign localized sclerosing types and generalized cellular sarcomatous types is difficult to apply to the few cases of Hodgkin's disease in which the cutaneous lesions are specific. Apparently the paragranulomatous type occurs most frequently in children and runs a relatively benign course over many years; the granulomatous type terminates fatally within ten years and the sarcomatous type which occurs chiefly in the later decades of life usually terminates within three years after the onset. Kierland and I, however, reported a case in which the patient who was eighteen years of age had had Hodgkin's disease of the supraclavicular lymph nodes for ten months and specific cutaneous nodulo ulcerative metastatic lesions of the thorax for six weeks.

A generalized *nonspecific toxic pruritus* with or without excoria-

tions and secondary papulopustular eruptions with or without residual pigmentation are the most common manifestations of Hodgkin's disease According to Longcope the pruritus has no relation to enlargement of the lymph nodes There may be diffuse pigmentation which may be the result of involvement of the chromaffin system[107] or may follow roentgen therapy or the ingestion of arsenic Transitory urticaria and lymphedema and even a scarlatiniform eruption may occur Local or generalized herpes zoster is common in cases in which the patients are in the later decades of life This occasionally results from direct and specific involvement of the roots of the spinal nerves Purpuric and hemorrhagic lesions or involvement of mucous membranes is not common

Hodgkin's disease may start as an exfoliative dermatitis or generalized erythroderma and the histopathological changes may be specific for lymphoblastoma but not for Hodgkin's disease per se[77] Exfoliative dermatitis is not as common a manifestation however in my experience as Epstein and MacEachern have maintained Specific cutaneous changes may be manifested by groups of nodules or ulcers The ulcerative forms of the disease have been divided into three types[16] (1) small ulcers arising from nodules ( ) ulcers resulting from extension from underlying lymph nodes or other structure and (3) primary cutaneous ulcers These ulcers frequently have been diagnosed erroneously In the case reported by Kren the disease was diagnosed as a sarcoma the leg was amputated and the correct diagnosis was made at necropsy which was performed four years later On the other extreme in a case of multiple deep seated nodules the disease was regarded as relapsing febrile nodular nonsuppurative panniculitis of Weber Christian and the diagnosis of Hodgkin's disease was made at necropsy[6] Thus the cutaneous infiltration of Hodgkin's disease may not present a diagnostic clinical picture

Because Hodgkin's disease may simulate clinically the picture of mycosis fungoides some authors would designate mycosis fungoides as a cutaneous manifestation of Hodgkin's disease[1] but the two conditions frequently run different courses and remain independent Again all transitions between Hodgkin's disease and other types of lymphoblastoma may be encountered The concomitant finding of Hodgkin's disease and cutaneous tuberculosis is extremely uncommon in contrast to the not infrequent association of systemic tuberculosis and Hodgkin's disease Hodgkin's disease of the lymph nodes or internal organs has

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been reported in association with generalized torulosis (cryptococcosis)[31] and in several instances with histoplasmosis [76]

Pathology — I am in accord with Jackson and Parker and other authors who require demonstration of Reed-Sternberg cells (Fig 5*d*) for a diagnosis of Hodgkin's disease In the skin, however possibly as a result of distortion from fixation mononucleated or multinucleated Reed Sternberg cells are not as distinctive as they are when seen in the lymph nodes or other organs There is likely to be some distortion in the shape and size of the cells, but these cells can nevertheless be distinguished from the pseudoclumping of cells seen in mycosis fungoides (Fig 5*e*) Furthermore eosinophilia or areas of necrosis are not necessarily present in the cutaneous lesions and the infiltrate in the cutis may be chiefly lymphocytic in type with only a few reticulum cells but with definite Reed Sternberg cells As a rule however, the pathological picture of Hodgkin's disease of the skin parallels that seen in the internal organs and varies according to the stage of the disease Areas of fibrosis and necrosis in the cutis can be distinguished from those secondary to previous radiotherapy by evidence of obliterative changes in the vessels and a loss of dermal appendages in the latter condition Epidermal changes usually are minimal but in regions of ulceration they simulate changes seen in mycosis fungoides Tissue eosinophilia is seen in many types of benign inflammatory dermatosis[11] as well as in Hodgkin's disease It also occurs in so called eosinophilic granuloma of the skin[23, 116], which in some cases may represent an aberrant type of Hodgkin's disease and in other cases apparently is an expression of a benign allergic reaction[10] Nodules and tumors the result of certain insect bites, especially the bites of ticks chiggers and mosquitoes may persist for many years and histopathologically closely simulate Hodgkin's disease with eosinophilia, necrosis and multinucleated giant cells or at times may simulate the changes of leukemia cutis[1, 8]

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Leukemia Cutis

Leukemia cutis may be divided into the lymphatic myelogenous and monocytic types The last type is subdivided into the Naegeli and Schilling types including reticulo endotheliosis *Lymphodermia perniciosa* (Kaposi) is an old term that has been used to designate an ill defined condition belonging either with leukemia or mycosis fungoides The term leukemid formerly used to designate a shower of lesions is rarely employed today Acute or chronic leukemia of various types may be encountered at any age and affects males more frequently than it affects females Rapidly fulminating types with or without cutaneous lesions are seen among children A primary autochthonous origin is encountered most frequently in cases of chronic lymphatic leukemia but also occurs frequently in monocytic leukemia especially in the exfoliative or erythrodermic forms and has been observed in cases of myelogenous leukemia In the majority of cases leukemia cutis is secondary to metastasis or extension from within There is great variation in regard to rapidity of the course and some of the cutaneous forms of chronic lymphocytic and monocytic leukemia may persist for many years Transition of leukemia to other forms of lymphoblastoma is as frequent as is the transition of mycosis fungoides to Hodgkin s disease

In acute leukemia cutaneous manifestations are frequently of a non specific toxic character and include hemorrhages both petechial and diffuse involvement of both skin and mucous membranes ulcers and necrotic lesions Urticarial and hemorrhagic lesions frequently are a terminal manifestation

Chronic lymphatic leukemia the most common type with specific cutaneous involvement may appear as multiple discrete to diffuse lymphomatous nodules and tumors in the skin and subcutaneous tissue which at times may involve the mucous membranes The lesions vary in size number and distribution They sometimes simulate the lesions of sarcoidosis and at other times occur as nodular and diffuse edematous swelling of the face and simulate the leontiasic changes seen in leprosy or they simulate a severe angioneurotic edema or solid edema of the face Exfoliative dermatitis and erythroderma are relatively common and usually are accompanied by intense pruritus The skin may be reddish brown and resemble that seen in pityriasis rubra of Hebra which however is no longer regarded as a disease entity[5] There may be subsequent atrophy with poikiloderma like changes Herpes simplex rupial lesions[8]

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facial diplegia[4] and tuberculoid reactions[12] have been reported There frequently is an associated herpes zoster[98, 119], and the herpetic lesions may contain at times a specific leukemic infiltrate[6]

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Follicular lymphoblastoma which first was described as giant lymph follicle hyperplasia of the lymph nodes and spleen has come to be regarded by most writers as a lymphoblastoma Combes and Bluefarb reported 15 cases of giant follicular lymphadenopathy associated with cutaneous lesions In 5 of these cases a polymorphous cell sarcoma developed and in 4 cases the disease terminated fatally Cutaneous lesions included exfoliative dermatitis erythroderma chronic discoid lichenoid dermatitis of Sulzberger Garbe different types of eczema and mycosis fungoides which occured in 1 case Not all of their patients could be strictly classified as having follicular lymphoblastoma

Lymphocytoma of the skin which first was described by Jadassohn in 190- has been the subject of numerous reports, especially by Epstein and later by Hallam and Vickers The condition has also been designated as lymphadenosis miliary lymphocytoma or benign lymphadenoid granuloma of the skin The use of the term lymphocytoma to designate lesions of the skin must not be confused with the older broader use of the term to designate all types of lymphoblastoma Cutaneous lymphocytoma is characterized by miliary nodules which occur not only on the face but also on the ear scrotum labia and extremities and as a disseminate eruption The lesions clinically simulate miliary sarcoid or lupus miliaris disseminatus At times there are larger nodules or brownish red infiltrated plaques There are no hemocytological changes and whereas the possibility of these lesions being transformed into frank lymphoblastoma has been suspected there are as yet no reported cases in which a change has been proved to have occurred The tumors have been regarded as developing from pre existing lymphoid tissue in the skin There is a similarity between the histopathological changes of cutaneous lymphocytoma and those of the more benign types of follicular lymphoblastoma and even those of the paragranulomatous stage of Hodgkin s disease which suggests a close relation between these conditions

Pathology —The cutaneous changes in lymphosarcoma are similar to those seen in leukemia (Fig 4c) but are distinguished by the presence of numerous mitotic figures and by the absence as a rule of any hemo-

coma[10] So called Spiegler Fendt sarcoid[70] and some, if not all, follicular lymphoblastomas (giant follicle lymphomas[50]) and most cutaneous lymphocytomas represent variants of reticulum-cell and lymphocytic types of lymphosarcoma The older term 'leukosarcomatosis cutis of Sternberg', apparently was used to designate a lymphosarcoma that was associated with hemocytological evidence of leukemia There is still lack of uniformity regarding the terms used to designate the different types of lymphosarcoma Various types of lymphosarcoma may occur at any age The disease has a tendency to affect males more frequently than it does females but this tendency is not as marked as it is in other types of lymphoblastoma Lymphosarcoma may have a primary autochthonous, cutaneous origin and may run a relatively benign course as is true also of certain types of Spiegler-Fendt sarcoid cutaneous lymphocytoma[9] and follicular lymphoblastoma Usually the cutaneous involvement is secondary to involvement of lymph nodes or other organs and usually the course is a rapidly progressive and fatal one, especially in children Cutaneous lymphosarcoma of different types may be a terminal manifestation of any one of the lymphoblastomas

Primary autochthonous lymphosarcoma of the skin may occur as solitary or multiple nodules it rarely occurs in the form of exfoliative dermatitis or erythroderma Occasionally there is involvement of the mucous membranes

I have observed two cases of localized lymphosarcoma of the lymphocytic type in which there were a group of nodules on the back and in which there has been no recurrence in ten to twelve years after excision followed by radiotherapy This emphasizes the value of early diagnosis and radical excision which apparently holds true for lymphosarcoma in general[3 81 104]

Spiegler-Fendt sarcoid is a misnomer in that it has nothing to do with sarcoidosis but is a true sarcoma Lewis[70] divided this condition into localized and disseminate forms The localized form simulates miliary sarcoid but histologically is composed of mature lymphocytes and at times reticulum cells with occasional mitotic figures There are no associated hemocytological changes The lesions are found anywhere on the body, they may be few in number they may be solitary or grouped and their color may vary from red to the normal color of the skin They occasionally occur as infiltrated plaques There usually is no adjacent lymphadenopathy and the lesions undergo involution spontaneously or after arsenical or roentgen therapy This localized type

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ALLIED CONDITIONS AND DIFFERENTIAL DIAGNOSIS

Multiple, idiopathic, hemorrhagic sarcoma of Kaposi[7, 8] occurs as bluish nodules and plaques It usually occurs on the extremities but may involve the mucous membranes and be seen anywhere on the body The cutaneous lesions may simulate those seen in any type of lymphoblastoma The literature contains a report of a case in which Kaposi's sarcoma was associated with mycosis fungoides[67] and a report of a case in which lymphatic leukemia was associated with Hodgkin s disease[99] These transitions might be anticipated as Kaposi s sarcoma like mycosis fungoides starts as a benign, probably infectious process involves the reticulo endothelial system and finally produces angiosarcomatous or fibrosarcomatous changes both in the skin and internal organs

Differentiation of eosinophilic granuloma of the skin and Hodgkin's disease has already been considered In eosinophilic granuloma of bone which apparently is related to Hand Schuller Christian disease and to

Letterer Siwe disease and which is related to the reticulo-endothelial system in a broad sense the cutaneous lesions may occur as ulcerative and granulomatous lesions[48] which simulate some forms of lymphoblastoma but the two diseases can be distinguished by the pathological findings

Along with many other authors I formerly accepted the view that parapsoriasis especially the en plaque and possibly the variegata type was frequently a prodromal manifestation of one of the lymphoblastomas particularly mycosis fungoides As a result of studies which I made with Burkhart[49] however I am now convinced that with but very few exceptions parapsoriasis remains as such throughout the course of the disease Cases reported as parapsoriasis with transition to mycosis fungoides may have been cases of mycosis fungoides or some other type of lymphoblastoma from the beginning Microscopic examination of an early premycotic parapsoriasis like plaque will disclose that histopathological changes of mycosis fungoides already are present I therefore am in complete disagreement with Keil s views, including his criticisms and interpretations of our paper Further observations have amplified and confirmed the views which we expressed previously

It is important to distinguish leukemoid reactions from true lymphoblastoma In a case observed by Fraser (personal communication) in which the clinical diagnosis was mycosis fungoides and the hemocytological diagnosis was chronic lymphatic leukemia involution of the process followed cessation of exposure of the patient to benzol fumes In another of his cases exfoliative dermatitis followed the application of strong mercurial ointment and a diagnosis of *Hodgkin s disease* was made by microscopic examination of an enlarged inguinal lymph node He also reported[35] a case of exfoliative dermatitis in which hemocytological examination disclosed chronic lymphatic leukemia that disappeared spontaneously Heck and Hall described leukemoid reactions especially of the myeloid type which occurred in association with various infections and irritations of the bone marrow due to various causes *Mention is made here again of leukemoid reactions seen in* chronic insect bites[1, 2] Cannon has referred to a group of cases of allergic dermatitis in which the disease clinically simulated mycosis fungoides leukemia and Hodgkin s disease Conversely however I have seen lesions which were diagnosed eczema and chronic discoid lichenoid dermatitis clear up temporarily only to recur as one of the lymphoblastomas

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recur and then respond again to subsequent roentgen therapy The same observations can be made at the present time The technic of irradiation has varied somewhat in treating mycosis fungoides and other types of lymphoblastoma If the involvement is primarily cutaneous local treatment with suberythema doses of unfiltered or lightly filtered roentgen rays seems to produce the best results If the cutaneous involvement is extensive the patient should receive what colloquially might be termed an x ray bath Filtered irradiation directed toward the lymph nodes the spleen and other organs does not seem to cause involution of cutaneous lesions any more rapidly than does superficial irradiation of the cutaneous lesions themselves If there is evidence of systemic involvement or involvement of the lymph nodes filtered irradiation is indicated Systemic roentgen therapy must be employed with extreme caution in certain acute phases of various types of leukemia and should be con trolled carefully with hemocytological studies to avoid leukopenia anemia and various blood dyscrasias The response of cutaneous lesions to roentgen therapy varies not only according to the type of lympho blastoma and the acuity of the process but also according to the amount of treatment that has been given in the past In many cases roentgen therapy appears to lose its effectiveness after a period of months or years and the cutaneous lesions seem to become resistant even to increased doses of roentgen rays As previously mentioned in the case reports under mycosis fungoides the use of fever therapy and chaulmestrol (first suggested by Lomholt) may result in temporary benefit and also apparently may alter the patient s response to roentgen therapy These forms of treatment were instigated by Klauder and then by O Leary and by other physicians[87] on the basis that lymphoblastomas are concerned primarily with the reticulo endothelial system What has just been said regarding roentgen therapy is equally applicable to the use of radium in various forms of localized lesions

Recently temporary partial or complete involution of mycosis fungoides and other types of lymphoblastoma has resulted from the administration of nitrogen mustard[15 5 65 89 93 10] The drug is to be given intravenously usually in daily doses of 0 1 mgm per kilogram of body weight for four days There is a tendency to use a smaller dose because severe toxic effects such as leukopenia aplastic anemia and other blood dyscrasias have occurred in some cases Like various other forms of therapy nitrogen mustard appears to have only a transitory effect and it is anticipated that in the future there will be newer drugs that will not

Distinction of lymphoblastoma from sarcoid or nodules and tumors associated with leprosy and other granulomas or with metastatic neoplasms other than lymphoblastoma is readily made by the concomitant histopathological findings

Prognosis

Any type of lymphoblastoma almost invariably terminates fatally The duration of life however varies greatly depending on the type and extent of the lymphoblastomatous involvement Life may be prolonged for many years by judicious therapy [1], especially roentgen therapy When the process is confined primarily to the skin, the prognosis usually is better than it is when cutaneous manifestations are secondary to systemic involvement Spontaneous involution without treatment may occur in some cases of exfoliative dermatitis, mycosis fungoides and occasionally in other localized cutaneous forms of chronic lymphoblastoma In such cases however cutaneous and systemic manifestations of one of the lymphoblastomas almost invariably develop within a period of months or years Lymphocytoma cutis runs a relatively benign course while acute leukemia and lymphosarcoma usually are rapidly fatal Between these two extremes in order of increasing severity, are mycosis fungoides Hodgkin's disease, Spiegler-Fendt sarcoid chronic leukemia and lymphosarcoma In cases of leukemia and lymphosarcoma in which the patients are children the disease usually runs a very rapid and malignant course The course of Hodgkin's disease varies according to the type of the disease In any type of lymphoblastoma secondary cutaneous manifestations which appear late in the course of the disease especially acute toxic manifestations including purpuric and hemorrhagic lesions are often indicative of a rapidly progressive phase and an early fatal termination

Treatment

Since the beginning of this century, roentgen therapy has been employed in the treatment of mycosis fungoides and other types of lymphoblastoma In 1904 Hyde and Montgomery said that roentgen therapy caused the cutaneous lesions of mycosis fungoides including tumors to melt away over varying periods of time The lesions would

ridyl] ethylenediamino) and similar drugs in the treatment of toxic urticarial reactions

Summary

Cutaneous manifestations of any of the pathological conditions classified under the term lymphoblastoma, whether they are specific or nonspecific in type have been reported as occurring in from 10 to more than 40 per cent of all cases of lymphoblastoma. Recognition of these cutaneous manifestations may often be of distinct value in arriving at the correct diagnosis in a given case. Clinical and histopathological study of cutaneous manifestations should be correlated with comprehensive general systemic studies including roentgenological pathological and hemocytological studies. Skin smears made from specimens removed for biopsy are also of diagnostic value. Diagnosis of the type of lymphoblastoma often may be made only after a long period of observation. There apparently is a very close relationship between the various forms of lymphoblastoma but until more is known regarding their cause diagnosis of the type of lymphoblastoma should be made whenever possible. Prognosis is dependent on the extent of involvement the acuity of the process and the type of lymphoblastoma but in a given case death occurs in from several months to as long as forty or more years after the onset of the disease. Palliative treatment with roentgen therapy remains the treatment of choice but this may be supplemented in certain cases by other methods of treatment

produce such severe toxic effects The use of nitrogen mustard seems valuable for patients who have received the limit of tolerance for roentgen therapy or for patients who have become relatively resistant to roentgen therapy In the latter group once a patient has had nitrogen mustard he may subsequently respond to further roentgen therapy

One of the reasons that improvement in the cutaneous lesions of different types of lymphoblastoma is only temporary may be that speci mens for biopsy even of lesions that have undergone complete involu tion still reveal histopathological evidence of lymphoblastoma in ques tion In the majority of cases there is little change in the histopathological picture after treatment with nitrogen mustard, although in a few instances pathological as well as clinical involution of the lesion occurs This parallels the findings of Cornell and Blauw in Hodgkin's disease in organs other than the skin

Various radioactive isotopes have not been found particularly valu able in the treatment of cutaneous lymphoblastoma Urethane and aminopterin have not had sufficient trial Zarafonetis Curtis and Grekin and later Zarafonetis reported improvement in cutaneous lesions from the administration of para aminobenzoic acid (PABA) Garb[41] has studied the use of preparations of antimony in the treatment of mycosis fungoides and obtained good results from injections of tartar emetic sodium antimony in the form of fuadin and stibanose but in only three of ten cases

Surgical excision of localized cutaneous nodules as stated earlier, resulted in cure in two cases of lymphosarcoma and no evidence of recurrence has been observed for ten years and twelve years respec tively in these cases Surgical excision of fungating tumors may be indicated for palliative relief In reported cases of localized forms of Spiegler Fendt sarcomas and occasionally in reported cases of Hodgkin's disease surgical excision or intensive radiotherapy[21, 51] has been said to have produced a cure An intense pruritus accompanies the specific and nonspecific cutaneous manifestations of most types of lymphoblastoma Various bland and antipruritic lotions and ointments including those containing 1 to 2 per cent of phenol or menthol may afford temporary relief as may also preparations containing derivatives of cocaine The oral administration of acetylsalicylic acid or of various barbiturates is sometimes of value as is also the use of benadryl (diphenhydramine hydrochloride) pyribenzamine (N N dimethyl-N -benzyl N [α py-

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17 COMBES F C and BLULFARB S M Giant follicular lymphadenopathy Arch Dermat and Syph 1941 XLIV 409
18 Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood Forming Organs Recommended terms and definitions for cells of the leukocytic erythrocytic and thrombocytic series Jour Am Med Assoc 1949 CXXXIX 17
19 CORNELL V H and BLAUW A S Histopathologic observations in cases of Hodgkins disease treated with nitrogen mustard Am Jour Path 1949 XXV 33
o COTTINI J Aspects hematologiques et histopathologiques de trois cas de mycosis fongoide Ann de Dermat et de Syph 1937 7 S VIII 15
21 CRAVER L F Lymphomas and leukemias Jour Am Med Assoc 1948 CXXXVI 44
2 CURTIS A C and GRLKIN J N Histoplasmosis Jour Am Med Assoc 1947 CXXXIV 1 17
2, DOBLS W L and WEIDMAN F D Granulomatous Hodgkins disease of the skin with extreme eosinophilia Arch Dermat and Syph 1947 LV 1
24 DOWNEY H Handbook of Hematology Paul B Hoeber Inc New York 1938
25 DÖRFFEL J Histogenesis of multiple idiopathic hemorrhagic sarcoma of Kaposi Arch Dermat and Syph 1932 XXVI 608
26 DOSTROVSKY A and SAGHER F Poikiloderma as the initial stage of mycosis fungoides Arch Dermat and Syph 1945 LI 182
27 ELLER J J and FOX E C Fatal iododerma Arch Dermat and Syph 1931 XXIV 745
28 EPSTEIN E and MacEACHERN K Dermatologic manifestations of the lymphoblastoma leukemia group Arch Int Med 1937 LX 867
9 EPSTEIN S Lymphocytome der Haut mit Beteiligung der Conjunctiva bulbi Arch f Dermat u Syph 1935 CLXXIII (Pt) 13
30 FISCHLR WASELS B Experimentelle Grundlagen und Folgerungen der Regenerationstheorie der Geschwulstbildung Klin Wochnschr 193 XI 1937 1977 Editorial Jour Am Med Assoc 1934 CII 214
31 FITCHETT M S and WEIDMAN F D Generalized torulosis associated with Hodgkins disease Arch Path and Lab Med 1934 XVIII 25
3 FRASER J F The pathology of mycosis fungoides (older lit) Jour Cutan Dis 1917 XXXV 793
33 FRASER J F The interpretation of mycosis fungoides as a variety of lymphosarcoma Arch Dermat and Syph 1925 XI 4 5

BIBLIOGRAPHY

1 ALLEN A C Persistent insect bites (dermal eosinophilic granulomas) simulating lymphoblastomas histiocytoses and squamous cell carcinomas Am Jour Path (4 367–387 (Mar) 1948

2 ARZT L and FUHS H Hauterkrankungen bei Leukosen und Leukoblastomen sowie verwandten Zustanden LXXXI pp 1 173 In Jadassohn J Handbuch der Haut- und Geschlechtskrankheiten Julius Springer Berlin 19 9

3 ASH J E and SPITZ S Pathology of Tropical Diseases p 3 5 W B Saunders Company Philadelphia 1945

4 AUSPITZ H Ein Fall von Granuloma fungoides Viertljahrschr f Dermat u Syph 1885 XXII 1 3

5 BARNEY R F Pityriasis rubra (Hebra) Arch Dermat and Syph 19 8 XVIII 716

6 BARTON R L and O LEARY P A Herpes zoster generalisatus associated with chronic lymphatic leukemia Arch Dermat and Syph 1945 LI 63

7 BECKER S W and THATCHER H W Multiple idiopathic hemorrhagic sarcoma of Kaposi Jour Invest Dermat 1938 I 379

8 BERMAN L Pathologic nature of mycosis fungoides Arch Path 1940 XXIX 530

9 BERTACCINI G Über eine noch nicht beschriebene Hauterscheinung (Rupia) im Verlaufe einer chronischen leukämischen Lymphadenoma Dermat Wochnschr 1934 XCVIII 741

10 BURLEY H M Eosinophil granuloma of the skin Jour Invest Dermat 1946 VII 91

11 BURKHART R J and MONTGOMERY H Dermatologic significance of tissue eosinophilia Arch Dermat and Syph 1944 XLIX 19

12 BUSMAN G J and WOODBURNE A R Lymphatic leukemia with generalized follicular eruption of tuberculomatous architecture Jour Am Med Assoc 1930 XCV 1253

13 CAILLIAU F A propos de l histogenese du mycosis fongoide Ann de Dermat et de Syph 1938 7 S IX 857

14 CALLENDER G R Tumors and tumor like conditions of the lymphocyte the myelocyte the erythrocyte and the reticulum cell Am Jour Path 1934 X 443

15 CANNON A B Allergic dermatitis simulating lymphoblastoma Arch Dermat and Syph 1939 XXXIX 846

16 COLE H N The cutaneous manifestations of Hodgkin s disease lymphogranulomatosis Jour Am Med Assoc 1917 LXIX 341

17 COMBES F C and BLUEFARB S M Giant follicular lymphadeno pathy Arch Dermat and Syph 1941 XLIV 409
18 Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood Forming Organs Recommended terms and definitions for cells of the leukocytic erythrocytic and thrombocytic series Jour Am Med Assoc 1949 CXXXIX 175
19 CORNELL V H and BLAUW A S Histopathologic observations in cases of Hodgkins disease treated with nitrogen mustard Am Jour Path 1949 XXV 233
20 COTTINI J Aspects hematologiques et histopathologiques de trois cas de mycosis fongoide Ann de Dermat et de Syph 1937 7 S VIII 15
1 CRAVER L F Lyphomas and leukemias Jour Am Med Assoc 1948 CXXXVI 244
CURTIS A C and GREKIN J N Histoplasmosis Jour Am Med Assoc 1947 CXXXIV 1 17
23 DOBES W L and WEIDMAN F D Granulomatous Hodgkins disease of the skin with extreme eosinophilia Arch Dermat and Syph 1947 LV 1
4 DOWNEY H Handbook of Hematology Paul B Hoeber Inc New York 1938
5 DORFFEL J Histogenesis of multiple idiopathic hemorrhagic sarcoma of Kaposi Arch Dermat and Syph 193 XXVI 608
26 DOSTROVSKY A and SAGHER F Poikiloderma as the initial stage of mycosis fungoides Arch Dermat and Syph 1945 LI 18
27 ELLER J J and FOX E C Fatal iododerma Arch Dermat and Syph 1931 XXIV 745
8 EPSTEIN E and MacEACHERN K Dermatologic manifestations of the lymphoblastoma leukemia group Arch Int Med 1937 LX 867
9 EPSTEIN S Lymphocytome der Haut mit Beteiligung der Con junctiva bulbi Arch f Dermat u Syph 1935 CLXXIII (Pt) 13
30 FISCHER WASELS B Experimentelle Grundlagen und Folgerungen der Regenerationstheorie der Geschwulstbildung Klin Wochnschr., 193 XI 1937 1977 Editorial Jour Am Med Assoc 1934 CII 14
31 FITCHETT M S and WEIDMAN F D Generalized torulosis associated with Hodgkins disease Arch Path and Lab Med 1934 XVIII 225
3 FRASER J F The pathology of mycosis fungoides (older lit) Jour Cutan Dis 1917 XXXV 793
33 FRASER J F The interpretation of mycosis fungoides as a variety of lymphosarcoma Arch Dermat and Syph 19 5 XI 4 5

34 FRASER J F Mycosis fungoides its relation to leukemia and lymphosarcoma Arch Dermat and Syph 19 5 XII 814

35 FRASER J F Exfoliative dermatitis Arch Dermat and Syph., 1943 XLVIII 4

36 FREEMAN H E and KOLETSKY SIMON Cutaneous lesions in monocytic leukemia Arch Dermat and Syph 1939 XL 18

37 GALL E A and MALLORY T B Malignant lymphoma Am Jour Path 1942 XVIII 381

38 GANS O The skin picture in hematopoietic diseases, Arch Dermat and Syph 19 XXI 1

39 GANS O Histologie der Hautkrankheiten, pp 557-586 Julius Springer Berlin 19 8

40 GARB JOHN Mycosis fungoides with bullous lesions Arch Dermat and Syph 1944 XLIX 315

41 GARB JOHN Antimony preparations in the treatment of mycosis fungoides Jour Invest Dermat 1949 XIII 95

42 GARVEY P H and LAWRENCE J S Facial diplegia in lymphatic leukemia Jour Am Med Assoc 1933 CI 1941

43 GATES OLIVE Cutaneous tumors of leukemia and lymphoma, Arch Dermat and Syph 1938 XXXVII 1015

44 GOECKERMAN W H and MONTGOMERY, H Cutaneous lymphoblastoma report of two unusual cases Arch Dermat and Syph 1931 XXIV 383

45 GOLDBERG L C and MASON L M Treatment of cutaneous blastomas and other diseases with nitrogen mustard Arch Dermat and Syph 1949 LX 181

46 GOLDMAN L B Hodgkins disease Jour Am Med Assoc 1940 CXIV 1611

47 GOLDSMITH, W N Reticuloses Brit Jour Dermat and Syph 1944 LVI 107

48 HALLAM R and VICKERS H R Two cases of miliary lymphocytoma or benign lymphadenoid granuloma of the skin Brit Jour Dermat 1939 LI 251

49 HECK F J and HALL B E Leukemoid reactions of the myeloid type Jour Am Med Assoc 1939 CXII 95

50 HELD, I W and CHASNOFF J Giant follicular lymphoblastoma (giant lymph follicle hyperplasia) Am Jour Med Sci 194-, CCIV 232

51 HELLWIG C A Malignant lymphoma the value of radical surgery in selected cases Surg Gynec and Obst 1947 LXXXIV 950

52 HENSTELL H H TOBER J N and NEUMAN B A The influence of nitrogen mustard on mycosis fungoides Blood 1947 II 564

53 HERXHEIMER K and MARTIN H Mycosis fungoides pp 174 70 in JADASSOHN J Handbuch der Haut und Geschlechts krankheiten Julius Springer Berlin, 19 9

54 HUBLER, W R and NETHERTON E W Cutaneous manifesta tions of monocytic leukemia Arch Dermat and Syph 1947 LVI 70

55 HYDE, J N and MONTGOMERY F H A Practical Treatise on Diseases of the Skin ed 7 Lea & Febiger Philadelphia 1904

56 JACKSON H Jr and PARKER F Jr Hodgkin s disease New England Jour Med 1944, CCXXX 1 CCXXXI 35 639 1945 CCXXXII 547 CCXXXIII 369 1946 CCXXXIV 37 103

57 JACKSON H and PARKER F Hodgkin s Disease and Allied Dis orders Oxford University Press, New York 1947

58 JEANSELME and BURNIER La forme verruqueuse et hyper keratosique du mycosis fongoide Ann de Dermat. et de Syph., 1926 VII 65

59 KAPOSI M Diseases of the Skin trans by J C Johnston p 593-603 Lecture XLVII William Wood & Company New York 1895

60 KEIM H L Universal leukemia cutis Arch Dermat and Syph 1924 X 579

61 KEIM H L The lymphoblastomas their interrelationships Arch Dermat and Syph 19 9 XIX 533

62 KELLER F Über die Mycosis fungoides der Schleimhaut und ihre Differential diagnose gegenuber Lues Inaugural Dissertation Hein rich Munch Frankfurt 1931

63 KETRON L W and GAY L N Universal lymphatic leukemia of the skin Bull Johns Hopkins Hosp 19 3 XXXIV 404

64 KIERLAND R R and MONTGOMERY HAMILTON Cutane ous ulcerative Hodgkin s disease Proceed Staff Meetings Mayo Clinic 1941 XVI 124 lit

65 KIERLAND R R., WATKINS C H and SHULLENBERGER C C The use of nitrogen mustard in the treatment of mycosis fungoides Jour Invest Dermat 1947 IX 195

66 KYRLE, J Histo biologie der menschlichen Haut und ihrer Er krankungen Ed pp 65 82 Julius Springer Berlin 19 7

67 LANE, C G and GREENWOOD A M Lymphoblastoma (my cosis fungoides) and hemorrhagic sarcoma of Kaposi in the same person Arch Dermat and Syph 1933 XXVII 643

*68 LAYMON C W and SEVENANTS J J The cutaneous manifes*tations of systemic reticulo-endothelial granuloma, Arch Dermat and Syph (in press)

69 LEVIN O L and BEHRMAN H T Roentgen ray therapy of mycosis fungoides Arch Dermat and Syph 1945 LI 307

34 FRASER J F Mycosis fungoides its relation to leukemia and lymphosarcoma Arch Dermat and Syph 1925 XII 814
35 FRASER J F Exfoliative dermatitis Arch Dermat and Syph, 1943 XLVIII 42
36 FREEMAN H E and KOLETSKY SIMON Cutaneous lesions in monocytic leukemia Arch Dermat and Syph 1939 XL 218
37 GALL E A and MALLORY T B Malignant lymphoma, Am Jour Path 1942 XVIII 381
38 GANS O The skin picture in hematopoietic diseases Arch Dermat and Syph 1927 XVI 1
39 GANS O Histologie der Hautkrankheiten pp 557 586, Julius Springer Berlin 1928
40 GARB JOHN Mycosis fungoides with bullous lesions Arch Dermat and Syph 1944 XLIX 315
41 GARB JOHN Antimony preparations in the treatment of mycosis fungoides Jour Invest Dermat 1949 XIII 295
42 GARVEY P H and LAWRENCE J S Facial diplegia in lymphatic leukemia Jour Am Med Assoc 1933 CI 1941
43 GATES OLIVE Cutaneous tumors of leukemia and lymphoma, Arch Dermat and Syph 1938 XXXVII 1015
44. GOECKERMAN W H and MONTGOMERY, H Cutaneous lymphoblastoma report of two unusual cases Arch Dermat and Syph 1931 XXIV 383
45 GOLDBERG I C and MASON L M Treatment of cutaneous blastomas and other diseases with nitrogen mustard Arch Dermat and Syph 1949 LX 181
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47 GOLDSMITH W N Reticuloses Brit Jour Dermat and Syph 1944 LVI 107
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49 HECK F J and HALL B E Leukemoid reactions of the myeloid type Jour Am Med Assoc 1939 CXII 95
50 HELD I W and CHASNOFF J Giant follicular lymphoblastoma (giant lymph follicle hyperplasia) Am Jour Med Sci, 1942, CCIV 232
51 HELLWIG C A Malignant lymphoma the value of radical surgery in selected cases Surg Gynec and Obst 1947 LXXXIV 950
52 HENSTELL H H TOBER J N and NEUMAN B A The influence of nitrogen mustard on mycosis fungoides Blood 1947 II 564

86 OLIVER E A Mycosis fungoides report of three cases of the tumor d emblee type Arch Dermat and Syph 19 4 X 183

87 ORMSBY O S and MONTGOMERY H Diseases of the Skin Ed 7 pp 863 88 Lea & Febiger Philadelphia 1948

88 ORMSBY O S FINNERUD C W and APFELBACH C My cosis fungoides report of a case with autopsy Arch Dermat and Syph 1933 XXVII 631

89 OSBORNE L D JORDON J W HOAK F C and PSCHIERER F J Nitrogen mustard therapy in cutaneous blastomatous dis ease Jour Am Med Assoc 1947 CXXXV 11 3

90 OSGOOD L L Monocytic leukemia report of six cases and review of one hundred and twenty seven cases Arch Int Med 1937 LIX 931

91 PALTAUF R Die lymphatischen Erkrankungen und Neubildungen der Haut vol 4 pt 2 p 625 (p 693 MF) in Mracek F Hand buch der Hautkrankheiten A Holden Wien & Leipzig 1909

92 PAUL, J T and LIMARZI L R Specific cutaneous lesions in chronic myeloid leukemia Arch Dermat and Syph 194 XLV 897

93 PHILPOTT O S WOODBURNE, A R and WALDRIFF G A Nitrogen mustard in the treatment of mycosis fungoides Jour Am Med Assoc 1947 CXXXV 631

94 PORT Quoted by TILDEN G H So called mycosis fongoide Boston Med and Surg Jour 1885 CXIII 386

95 RABELLO F Jr PORTUGAL, H and CRUZ LIMA C Reticu losis aleucemicas un caso raro con sintomatologia cutanea semejante a una sarcomatosis multiple Rev argent dermatosif 1940 XXIX 509

96 REIMANN H A HAVENS W P and HERBUT P A Hodg kin s disease with specific lesions appearing first in the skin Arch Int Med 1942 LXX 434

97 ROBB SMITH A H T Reticular tissue and skin (literature) Brit Jour Dermat and Syph 1944 LVI 151

98 RYAN B I Herpes zoster Thesis University of Minnesota Gradu ate School 1945

99 SACHS W and GRAY M Kaposi s sarcoma and lymphatic leu kemia Arch Dermat and Syph 1945 LI 3 5

100 SCHOENHOF S Die Lymphogranulomatose der Haut p 271 in JADASSOHN J Handbuch der Haut und Geschlechtskrank heiten LXXXI vol VIII p 271 Julius Springer Berlin 19 9

101 SHELMIRE, B Hodgkin s disease of the skin South Med Jour 19 5 XVIII 511

70 LEWIS G M Spiegler Fendt sarcoid a clinical or histologic entity? Arch Dermat and Syph 1935, XXXI, 67
71 LOMHOLT S Antileprolbehandlung bei Mycosis fungoides Arch f Dermat u Syph 1934 CLXX 467
72 LOVE A A Manifestations of leukemia encountered in otolaryngologic and stomatologic practice Arch Otolaryng 1936 XXIII 173
73 LYNCH, F W Cutaneous lesions associated with monocytic leukemia and reticulo endotheliosis Arch Dermat and Syph, 1936 XXXIV 775
74 McCARTHY L Histopathology of Skin Diseases, pp 483 487 483 500 The C V Mosby Company St Louis 1931
75 MALLORY F B The Principles of Pathologic Histology pp 3 6-338 W B Saunders Company Philadelphia 1914
76 MILLER H E KEDDIE F M JOHNSTONE H G and BOSTICK W L Histoplasmosis Arch Dermat and Syph 1947, LVI 715
77 MONTGOMERY H Exfoliative dermatosis and malignant erythroderma the value and limitations of histopathologic studies Arch Dermat and Syph 1933 XXVII 53
78 MONTGOMERY H Histogenesis of basal cell epithelioma Radiology 1935 XXV 8
79 MONTGOMERY H Precancerous dermatosis and epithelioma in situ Arch Dermat and Syph 1939 XXXIX 387
80 MONTGOMERY H and BURKHART R J Parapsoriasis its relation to mycosis fungoides and tuberculosis Arch Dermat and Syph 1942 XLVI 673 (also p 950 Keil s criticism of paper)
81 MONTGOMERY H and O LEARY P A Micosis fungoide y linfoblastomas de la piel Rev argent de dermatosif 1939 XXIII 181
82 MONTGOMERY, H and WATKINS C H Monocytic leukemia Arch Int Med 1937 LX 51
83 MONTGOMERY H and WATKINS C H Exfoliative dermatitis as a manifestation of monocytic leukemia (Schilling) Minnesota Med 1938 XXI 636
84 NANTA A Dermatoses en rapport avec les troubles de l appariel hematopoietique (Hematodermies), vol 5 chap 5 pp 5-1 664 in Darier Sabouraud Gougerot Millan Pautrier Ravaut Sezary and Simon Clement Nouvelle Pratique Dermatologique Masson et Cie Paris 1936
85 NANTA A and CHATELLIER L Keloid lymphogranulomatosis of leukoplakia type lymphogranulomatous chancre Ann de Dermat et Syph 19 5 VI 68-

CHAPTER I B

SARCOIDOSIS
(BESNIER BOECK-SCHAUMANN DISEASE)

By WARFIELD T LONGCOPE

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103 SIGEL H Mycosis fungoides in the Negro Arch Dermat and Syph 1945 LII 18

104 STOUT A P Is lymphosarcoma curable? Jour Am Med Assoc 1942 CXVIII 968

105 SUGARBAKER E D and CRAVER, L F Lymphosarcoma A study of 196 cases with biopsy Jour Am Med Assoc, 1940 CXV 17 112

106 SWEITZER S E and WINER L H Ulcerative Hodgkins disease and lymph node imprints Arch Dermat and Syph 1945 LI 9

107 SYMMERS D The clinical significance of the pathological changes in Hodgkins disease The association of Hodgkins disease with pigmentation of the skin resembling acanthosis nigricans (case 10 p 174) Am Jour Med Sci 1924 CLXVII 157

108 SYMMERS D Mycosis fungoides as a clinical and pathologic non existent Arch Dermat and Syph 1932 XXV, 1

109 TZANCK A DREYFUSS A and LEVY S La ponction sternale dans le mycosis fongoide Sang 1938, XII 110

110 WALLHAUSER A Hodgkins disease Arch Path and Lab Med 1933 XVI 522 672

111 WARTHIN A S Lymphocytoma IV 956 Oslers Modern Medicine Lea & Febiges Philadelphia 1908

112 WARTHIN A S The neoplastic relationship of Hodgkins disease aleukemic and leukemic lymphoblastomas and mycosis fungoides Am Jour Path 19 7 III 551

113 WARTHIN, A S The genetic neoplastic relationships of Hodgkins disease aleukaemic and leukaemic lymphoblastoma and mycosis fungoides Ann Surg 1931 XCIII 153

114 WAYSON, J T and WEIDMAN F D Aleukemic reticulosis Arch Dermat and Syph 1936 XXXIV 755

115 WEBER F P A case of rapidly fatal mycosis (granuloma) fungoides Brit Jour Dermat and Syph 1918 XXX 7

116 WEIDMAN, F D The eosinophilic granulomas of the skin Arch Dermat and Syph 1947 LV 155

117 WEIDMAN F D and CUSTER R P The scope of the so called 'cutaneous lymphoblastomas in relation to lesions of the haematopoietic system Copia Ex II° Volumine Deliberationum IX=1 Congressus Internationalis Dermatologorum

118 WIENER K Skin Manifestations of Internal Disorders XXXII pp 511-533 C V Mosby St Louis 1947

110 WILE U J and HOLMAN H H Generalized herpes zoster associated with leukemia, Arch Dermat and Syph 1940 XLII 587
1 o WILE U J and STILES F J Clinical mutations in lymphoblastomas Jour Am Med Assoc 1935 CIV 532
1 1 WILSON G T The Cytology of Skin Smears Thesis University of Minnesota Graduate School 1949
122 WINER L H Mycosis fungoides benign and malignant reticulum cell dysplasia Arch Dermat and Syph 1947 LVI 480
1 3 WINTROBE, M M Clinical Hematology Chaps XVII and XVIII pp 666 786 Ed 2 Lea & Febiger Philadelphia 1946
1 4 WISEMAN B K Lymphatic leukemia important facts additive to its clinical and hematologic recognition Jour Am Med Assoc, 1942 CXVIII 100
1 5 ZARAFONETIS C J D Therapeutic possibilities of para aminobenzoic acid Ann Int Med 1949 XXX 1188
1 6 ZARAFONETIS C J D CURTIS A C and GREKIN R H Effects of para aminobenzoic acid in lupus erythematosus preliminary report, Univ Hosp Bull Ann Arbor 1947, XIII 122

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CHAPTER I B

SARCOIDOSIS (BESNIER-BOECK-SCHAUMANN DISEASE)

By WARFIELD T LONGCOPE

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Definition — A chronic relapsing infection of the reticuloendothelial system usually benign but widely distributed throughout the body affecting particularly the lymph nodes lung spleen skin bone

marrow and liver and characterized by solitary and conglomerate collections of epitheliod cells arranged in tubercle like formations

Synonyms — Lupus pernio (Besnier), sarcoid (Boeck), benignes miliar Lupoid (Boeck) Boeck's sarcoid, benign lymphogranulomatosis (Schaumann) ostitis tuberculosa multiplex cystoides (Jungling), maladie de Besnier Boeck Hutchinson Boeck s disease (Hunter)

History

The first description of the disease according to Hunter[1], was given by Jonathan Hutchinson in 1869 but in 1889 Besnier[2] published an elaborate account of a patient with large violaceous swellings on the nose ears and about the interphalangeal joints of the fingers He considered the condition different from that described by Hutchinson and called the disease lupus pernio' Boeck[3] in 1899 gave an account of one patient who showed an eruption on the face and back consisting of nodules with bluish centers Microscopical examination of the lesions disclosed a tissue bearing some resemblance to sarcoma and he therefore termed the disease sarcoid From subsequent studies of several other patients suffering from the same affection he[4] recognized the fact that the disease was not limited to the skin but also occurred in the lymph nodes and nasal mucosa Further pathological examinations led him to the belief that the process was a peculiar form of tuberculosis and he therefore changed the appellation to benignes miliar Lupoid

The subsequent disjointed manner in which information concerning this disease grew has been elaborated by Hunter[1] and by Snapper and Pompen[5] Bezancon and Labbe[6] pictured it as a peculiar form of miliary tuberculosis causing enormous swellings of the cervical and submaxillary lymph nodes while Kienbock[7] in the same year evidently mistook it for syphilis of the bone marrow and Jungling[8] in 1915 described the osseous changes under the designation of ostitis tuberculosa multiplex cystica' It was not until Schaumann[9] in 1917 published his report of three cases of lupus pernio which had been presented previously as a prize essay in 1914[10] that clarity was brought to this confused situation He recognized the fact that lupus pernio' and Boeck s sarcoid were manifestations of one and the same disease which might affect the skin, lymph nodes lungs spleen and bone marrow He emphasized the systemic nature of this condition and was impressed by the uniform and characteristic pathological lesions to differentiate it from Hodgkin s disease he called it 'lymphogranuloma benin'

In 1915 Kuznitzky and Bittorf[11] unfamiliar with Schaumann s work contributed an important paper on the pulmonary lesions of Boeck s sarcoid The most recent addition to the long list of apparently unrelated conditions which eventually have proved to be manifestations of sarcoid is the syndrome originally described by Heerfordt in 1909[1] as febris uveo-parotidea chronica This interesting syndrome was recognized as one form of sarcoid in 1936[13] [b] [6]

Since these early contributions so much has been written concerning sarcoid and its different manifestations that a vast literature has accumulated on the subject This has been discussed and reviewed in the articles and monographs by Schaumann[10b] [d] Kissmeyer[14] Pautrier[1], Volk[16] Pinner[17] Martenstein[18] Snapper and Pompen Hannesson[19] Leitner[20] and Freiman[?0] while an entire session of the Reunion Dermatologique at Strasburg in 1934 was devoted to a consideration of Boeck s sarcoid[2]

Etiology

Scandinavia is so to speak the home of Besnier Boeck Schaumann s disease but it occurs throughout Europe and in England More recently it has become familiar in the United States and Canada where it is found to be comparatively common Cases have also been reported from South America At the Johns Hopkins Hospital it has been possible to collect 90 cases that have been studied during the last 10 years

In Europe as might be supposed sarcoid is seen almost exclusively in the white race but in the United States it affects predominately the negro Amongst 75 reported cases in this country there were 63 negroes 11 whites and one North American Indian while in our series from the Johns Hopkins Hospital there were 73 negroes and only 17 whites This is in sharp contrast to Hodgkin s disease which is comparatively unusual in the negro

The disease may be encountered at any age but is most likely to make its first appearance in young people between the ages of 20 and 40 Half of the 200 patients upon whom Kissmeyer[14] collected data from the literature contracted the disease before the age of 30 Two thirds or 60 of our 90 patients were under the age of 31 and 19 of them were under the age of 21 Neither the aged nor the very young are however exempt for one of our patients was 77 years of age and another 80 while very young children are reported to have had the disease[6]

Both males and females are equally affected Our experience accords

with the general statistics for 48 of our patients were male and 42 female Occasionally Boeck's sarcoid is seen in two or more members of the same family [3, 1] Four members of one of our negro families suffered from sarcoid from which at least one died This suggests that the disease may be transmitted by direct contact although there is no further evidence to uphold such an idea According to Lomholt the disease occurs more frequently in rural than in urban populations and although other observers have not stressed this particular association it was noted that many of our patients lived in the country or worked on farms

One of the main points at issue concerning the etiology of sarcoid is its relation to tuberculosis This has arisen principally from the close resemblance which the pathological lesion bears to the miliary tubercle and the comparative frequency with which patients with sarcoid develop frank tuberculosis from which they often die A great number of extensive and painstaking researches have however failed to establish convincing proof that any form of the tubercle bacillus is the direct cause of sarcoid[14, 15, 1, 18, 8, 8]

Long and concentrated search through the tissues from innumerable cases of sarcoid have failed almost without exception to demonstrate tubercle bacilli in the lesions although an occasional investigator[17, 0] has found a few acid fast bacilli in a rare section The inoculations of material from many uncomplicated instances of sarcoid into guinea pigs rabbits mice pigs hamsters chickens pigeons and ducks have given negative results [8] It has been impossible also to cultivate tubercle bacilli on special media from these tissues or to obtain any type of growth from filtrates of this material inoculated on chick egg membranes[8] In the occasional instances in which tuberculosis has been reported to follow the inoculation of guinea pigs with material from patients with sarcoid it is not always certain that the disease was uncomplicated by tuberculosis[1, 4]

Emphasis always has been placed on the fact that the skin of these patients does not often give a positive reaction to the intracutaneous injection of tuberculin Kissmeyer[14] states that a positive tuberculin reaction was noted in only about 40 per cent of the reported cases and that a positive focal reaction was quite as unusual as the skin reaction Lomholt[20] found the tuberculin reaction negative in 72 per cent of his 49 cases We have obtained negative tuberculin reactions in 48 of 74 cases tested or in 64 8 per cent A negative or only slightly positive tuberculin reaction is now accepted as characteristic of the uncomplicated disease[17] and is said to occur more often than in the general pop

ulation of the same age Indeed patients may fail to respond to such large amounts of tuberculin as 10 to 15 mgm as was the case in 10 of Reisner's[31] 14 cases A negative tuberculin reaction was obtained in 9 of our cases to 10 0 mgm and in another 9 to from 1 0 to 3 0 mgm This refractory state alluded to by Jadassohn[33] as anergie has been ascribed to the production of antibodies to tuberculin or anticutins[6] Later observers[33] have been unable to demonstrate with regularity anticutins in the serum of these patients and Leitner[30] rejects this explanation and advances the thesis that the negative tuberculin reaction is the result of fixation and destruction of antibodies at the site of their origin in the reticuloendothelial system by antigens of the tubercle bacillus

Anergie to tuberculin is by no means specific for sarcoidosis Suppression of the tuberculin reaction is common in Hodgkin's disease[34] and has long been known to occur in measles The latter fact led Pautrier to argue against the tuberculous origin of sarcoid

When patients suffering from sarcoidosis contract tuberculosis a negative reaction changes to positive and the skin may become exquisitely sensitive to tuberculin Minor changes in the same direction or from positive to negative may take place also without obvious reason[31, 35] It is noteworthy as Schaumann[10d] originally observed that the lesions of sarcoid are often regressing or in the healing stage at the time that tuberculosis supervenes

Frank tuberculosis is not an uncommon cause of death particularly in pulmonary sarcoidosis for it has been recorded in from 14 to [illegible] per cent of autopsies in some series[17, 31] Of the 14 fatal cases in our series of 90 patients 1[illegible] came to autopsy and 3 of these were found to have died of actively progressive tuberculosis

Many explanations have been offered to overcome the obvious discrepancies in assigning the etiology of sarcoidosis to tuberculosis It has been held that sarcoidosis represents a proliferative stage of human tuberculosis that the disease is due to the bovine type to an atypical modified or relatively benign form of the tubercle bacillus to a filterable variety or to the products of its growth such as a phosphatide The latter substance derived from tubercle bacilli has been shown by Sabin[6] to call forth upon injections in animals the production of epithelioid cells and giant cells that may assume the arrangement of tubercles

Though rejecting the idea that sarcoidosis is tuberculosis some investigators are inclined to attribute its etiology to another form of acid fast bacillus Kissmeyer and Nielsen[5] impressed by the resemblance between the pathological lesions of leprosy and those of sarcoid

with the general statistics for 48 of our patients were male and 42 female. Occasionally Boeck's sarcoid is seen in two or more members of the same family.[3, 4] Four members of one of our negro families suffered from sarcoid from which at least one died. This suggests that the disease may be transmitted by direct contact although there is no further evidence to uphold such an idea. According to Lomholt[5] the disease occurs more frequently in rural than in urban populations and although other observers have not stressed this particular association it was noted that many of our patients lived in the country or worked on farms.

One of the main points at issue concerning the etiology of sarcoid is its relation to tuberculosis. This has arisen principally from the close resemblance which the pathological lesion bears to the miliary tubercle and the comparative frequency with which patients with sarcoid develop frank tuberculosis from which they often die. A great number of extensive and painstaking researches have, however, failed to establish convincing proof that any form of the tubercle bacillus is the direct cause of sarcoid.[14, 15, 17, 19, 20, 6]

Long and concentrated search through the tissues from innumerable cases of sarcoid have failed almost without exception to demonstrate tubercle bacilli in the lesions, although an occasional investigator[1, 9] has found a few acid fast bacilli in a rare section. The inoculations of material from many uncomplicated instances of sarcoid into guinea pigs, rabbits, mice, pigs, hamsters, chickens, pigeons and ducks have given negative results.[6, 8] It has been impossible also to cultivate tubercle bacilli on special media from these tissues or to obtain any type of growth from filtrates of this material inoculated on chick egg membranes.[8] In the occasional instances in which tuberculosis has been reported to follow the inoculation of guinea pigs with material from patients with sarcoid it is not always certain that the disease was uncomplicated by tuberculosis.[17, 9]

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number of autopsies performed on patients dying of this disease is comparatively small Recent statistics place the number at 44[4, 46] There were 14 deaths in our series with autopsies in 1[illegible] cases In many instances however a totally unrelated disease such as acute intestinal obstruction or meningococcus meningitis kills the patient and the lesions of sarcoid are found by accident at autopsy This occurred in 7 of our 1[illegible] cases and in 5 of Nickerson's[17] 6 cases Considerable attention has been paid to the fact that tuberculosis may be the cause of death but Hogan[11] found this to be true in only 5 of the 44 autopsies that he reviewed in the literature Three of our patients died from tuberculosis

The extent of the disease may vary greatly On the one hand it may be limited to a few lymph nodes or on the other it may be scattered widely affecting many organs The lymph nodes usually but not always are much enlarged and the other organs of the body may show a seeding of tiny grey specks and nodules or be the seat of tumor-like masses that sometimes reach considerable size These large masses have been seen most often in the mediastinum the lungs the heart the spleen and the liver They do not show caseation or necrosis The most common finding is the presence of grey or white granules studding the surface of the affected organ They may be mistaken readily for miliary tubercles or carcinoma

No organ in the body and scarcely any tissue appears to be immune The lymph nodes are involved with great regularity and even though they are not enlarged they may show microscopic lesions No particular group shows any noticeable susceptibility The respiratory tract is another frequent seat of the disease The larynx the trachea the bronchi and pleurae may be involved occasionally but the lungs are affected very often either by miliary lesions by confluent masses or by a combination of the two Bilateral enlargement of the hilar lymph nodes is common This gives rise to a rather characteristic radiographic picture In rare instances cavities have been formed Tubercle bacilli have not been found in scrapings from the walls of these excavations

The pericardium and myocardium sometimes are extensively invaded by infiltrating masses of sarcoid tissue[48, 49] a condition quite unlike tuberculosis The spleen and liver both are prone to show sarcoid usually in the miliary form but sometimes as conglomerate masses These may cause enormous enlargement of the spleen or in rare instances a variety of portal cirrhosis[0] in the liver as happened in two of our patients Changes simulating sarcoid have been found in the esophagus stomach and other portions of the gastrointestinal tract and it is believed by some

suggest that the latter disease is caused by an organism nearly allied to the lepra bacillus.

The suggestion has been advanced by Pautrier[1] that the disease may be *due to infection by a virus*. Williams and Nickerson[38], who obtained what they believed to be specific skin reactions to extracts of sarcoid tissue in patients with sarcoidosis, held the same view. Kveim[39] recently has elaborated this method of study and considers that the disease is a specific infection unrelated to tuberculosis. The results of his investigations have been confirmed by Danbolt and Nilssen[40], but Lomholt[41] and Putkonen[1] have questioned the specificity of the reaction, since it could be produced by other unrelated antigens.

There is no indication that syphilis plays any part in the etiology. Occasionally reference is made to a resemblance between lymphopathia venereum and sarcoidosis, but the Frei reaction usually is negative as it was in 7 of 8 of our cases that were tested. Forms of bacteria such as brucella have been excluded as etiological factors. It is well known that *a number of agents including foreign bodies and beryllium[43] poisoning[44]* may give rise to a proliferation of epithelioid cells in the skin and lungs simulating in some respects the lesions of sarcoid. Leishmania may do so, but these organisms have not been found in sarcoid.[1]

It has been pointed out that trauma may precede the appearance of sarcoid[19]. This was a noticeable feature in one of our patients, who attributed the cutaneous lesions to an injury of the foot.

Although many arguments have been advanced in favor of the assumption that sarcoidosis is in some way nearly related to tuberculosis, if it is not actually a phase of tuberculosis, and although an expression of this attitude is popular, it nevertheless is desirable to withhold final judgment at the present time and consider that the etiology of sarcoidosis is unknown, for there are many features already referred to that are unlike tuberculosis. In addition to these the *distribution of the pathological lesions* is in some respects quite different from that seen in tuberculosis.

PATHOLOGY

Although Boeck's sarcoid was for years thought to be principally, if not exclusively, a disease of the skin, the cutaneous manifestations are now considered of subsidiary importance, for the generalized character of the condition outweighs in significance any regional localization of the process. Owing to the benign nature of sarcoidosis, however, the

the submaxillary and sublingual salivary glands are enlarged by deposits of sarcoid which have been found also in the thyroid parathyroids pancreas and adrenals

The remarkable clinical appearance of the extremities combined with the striking changes observed in X ray films of the bones in one group of cases has aroused interest in the pathological changes in the bones of these patients Comparatively few examinations have been possible They show that in the early changes minute grey bodies are scattered through the marrow and in the advanced stages areas of the cancellous bone are replaced by grey fibrous tissue The cortex may be thin and in some bones it is distorted but the joints escape injury

The microscopical character of the lesion in sarcoid is rather stereotyped and is repeated with almost monotonous regularity in one organ after another The smallest and probably the freshest lesions consist of a group of large pale epithelioid cells which show a tendency to tubercle like formation (Fig 1) They lie in the lymph nodes or various organs devoid of any peripheral inflammatory zone and without any evidence of central necrosis or caseation They may be completely isolated or arranged in groups of irregular formation At what appears to be a later stage the tubercle like formations become more definite Central necrosis and necrobiosis may be present but actual caseation is said not to occur and as Nickerson[1] has shown this central area of cell destruction is traversed by a network of fibrin a condition that is never seen in the caseating miliary tubercle At this stage the structures may be very numerous and grouped together over large areas that occupy the major portion of an enlarged lymphnode or that produce tumor like masses in various organs Even under these circumstances there is no tendency for the separate units to fuse for they preserve their identity throughout the entire course of their evolution

Giant cells are not uncommon and may be numerous They are often of great size and contain many deeply stained nuclei heaped together about the periphery or in the centre of the cell The remarkable inclusion bodies that are often seen within the giant cells have attracted much attention (Fig) Schaumann[1] was the first to emphasize their presence although probably they had been seen before They are referred to as Schaumann bodies Their size and shape varies but they may be very large almost filling the giant cells They stain deeply with hematoxylin and may contain crystalline like material or become conspicuous on account of the presence of calcified streaks and crescents Similar structures are extremely rare if they ever occur in the Langhans

that certain types of regional ileitis are caused by sarcoid Any portion of the genitourinary tract may be involved including the kidney, uterus seminal vesicles prostate testes spermatic cord and the endometrium

Since Boeck's original descriptions it has been known that the nasal mucosa may be the seat of sarcoid and Schaumann[100] stressed the fre



FIG 1 Section of lymph node showing collections of epithelioid cells arranged as miliary tubercles without central necrosis giant cells or surrounding zone of lymphoid infiltration

quency with which the tonsils are affected The faucial sinuses may be involved and infiltrations extend from the nasopharynx into the dura the meninges and brain Several instances are on record in which the hypothalamus was invaded and the pituitary gland destroyed

The eye and its surrounding structure seem to be particularly vulnerable for sarcoid has been described frequently in almost every tissue of the eye, in the lids and in the lacrymal gland The parotid and less often

be an accompanying infiltration of lymphocytes and plasma cells in the lung in the involved mucous membranes and in the internal organs

The process of healing takes place through the gradual transformation of the epithelioid structures into fibrous tissue which finally reduces

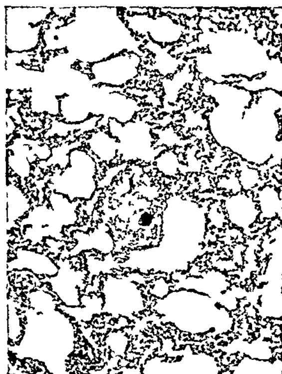


Fig 3 Showing epithelioid body in lungs Note lack of exudate in alveoli

them to a hyaline remnant only recognizable as the remains of a sarcoid when fresh lesions are seen in the same lymph node or organ

The tardy evolution of the distinctive lesion the unusual lack of any inflammatory reaction about it the pronounced tendency for healing to take place in one region with a recurrence of the disease months or years later in another situation are all features that have been emphasized over and over again

Though these lesions are readily recognizable and are characteristic of sarcoid they are by no means unique for they may be closely

giant cells of tuberculosis or in the Reed Sternberg giant cells of Hodg lin s disease They have been described, however, in foreign body reactions and in some other conditions but seem to be particularly characteristic of although not specific for, sarcoid



Fig Section of lymph node showing epithelioid body with large giant cell containing inclusion bodies

The peculiarity of the pathological lesion is its sluggish nature Lymph nodes enlarged for weeks or months may show on section only what appear to be fresh collections of epithelioid cells Another characteristic is the usual lack of inflammatory reaction in the organ or tissue involved This is a striking feature of the early pulmonary lesions (Fig 3) The groups of epithelioid cells are deposited in the interalveolar walls or in the walls of the finest bronchioles without the slightest evidence of an exudate of any sort in the alveoli or lumen of the bronchioles In the later stages when the invasion by sarcoid is extensive there may

connected with the eye (31 patients) or an enlargement of lymph nodes (19 cases) The remainder ranged over a wide field

From the very onset the disease pursues such an erratic and unpredictable course and is subject to such surprising recoveries and remissions with subsequent unaccountable relapses that any attempt to give a concise clinical description applicable in general to the malady is almost impossible As a rule it manifests itself as a combination or sequence of syndromes any one of which might be and indeed has been considered as a clinical entity It is therefore desirable to elaborate upon the features that may dominate at any one time remembering that they may occur in combination or in sequence

Lymph Nodes

One common characteristic at any stage is an involvement of one or another group of lymph nodes This varies from an enlargement of a few retroperitoneal periaortic or hilar lymph nodes discovered only at autopsy *to an enlargement of all the superficial and deep lymph nodes* in the body Either one of these extremes is rare Participation of one or another group of lymph nodes was however observed in 84 of our 90 patients and in [illegible] of them there was generalized swelling of the superficial nodes In all of Reisner s[31] 35 cases the peripheral lymph nodes were *affected*

The cervical axillary and inguinal groups are most likely to be involved but the submaxillaries also are rather *frequently* swollen and they give rise to the formation of a lumpy collar beneath the jaws and about the ears (Fig 4) The individual nodes may vary in size from some just palpable to others 3 *or* 4 *centimeters in* diameter They are entirely separate fairly firm can be readily moved and usually are not *tender* Unlike tuberculous *lymph nodes* there is no evidence of inflammatory reaction They are not adherent to the skin and do not ulcerate In this they resemble the lymph nodes of Hodgkin s disease

The intrathoracic and particularly the hilar lymph nodes share very frequently in this enlargement but they are only detectable by x ray or at autopsy (Fig 5) *Involvement of these groups* occurred *in* 30 *of* Reisner s[31] *cases and in 69 of ours* Bruce and Wassen[51] *consider* this the commonest intrathoracic lesion Although intrathoracic sarcoid may be restricted to the hilar lymph nodes producing bilateral oval shadows like a pair of small eggs at the roots of the lung there is sooner or later in many cases an associated lesion in the lung itself Shadows of various

simulated by the action of specific agents other than tuberculosis that are entirely unrelated to the etiology of sarcoid The early isolated reaction in the lymph nodes induced by brucellar infection may be almost exactly like the sarcoid[50a] The granuloma in the skin and lymph nodes that are caused by beryllium compounds bear a striking resemblance to sarcoid [1] Since these changes ascribed to beryllium may not appear for months or even years after the injury from the broken fluorescent bulb has taken place they may be readily confused with sarcoid

As Schaumann said originally sarcoid produces little or no toxic effect but injures through mechanical interference with the function of organs

Clinical Course

The onset of Besnier-Boeck-Schaumann's disease is generally so insidious that it may only be discovered for instance in a routine examination or casual x ray of the chest This was true of 1 of our 90 patients A careful analysis of the premonitory symptoms of the remainder however disclosed a variety of discomforts of which the patient complained on first seeking advice from a physician These complaints are listed in Table I The commonest of all was some trouble

TABLE I

Ocular disturbances	31
Enlarged lymph nodes	19
Loss of weight	14
Skin eruption	14
Cough	13
Shortness of breath	13
No symptoms	1
Abdominal pains	11
Swelling of parotid gland	5
Night sweats	4
Joint pains	4
Fatigue	4
Abdominal mass	3
Swelling of hands and feet	3
Facial paralysis	3
Pain in chest	2
Difficulty in swallowing	
Abdominal swelling	2
Hoarseness jaundice growth in nose and swollen testicle	1 each

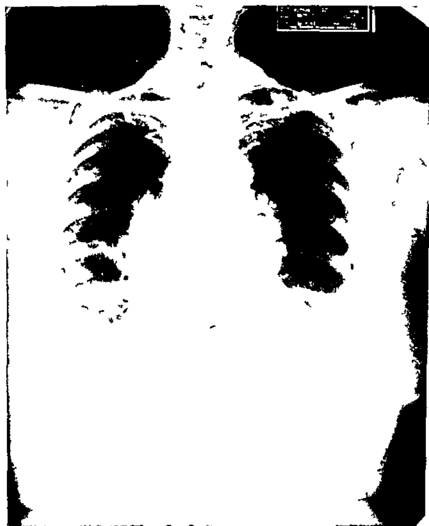


Fig 5 X ray showing bilateral enlargement of hilar lymph nodes

retroperitoneal nodes produced such huge tumors accompanied by so much abdominal pain that an exploratory operation was performed when the correct diagnosis was made from the histological examination of an excised lymph node

Other lymphoid structures appear to be particularly susceptible to

sizes may often be seen in the superior mediastinum presenting the appearance of tumors or lymphomata (Fig 6) These were noted in 10 of our cases Since many of these patients have few or no symptoms indicative of mediastinal growths, the intrathoracic masses and hilar nodes usually are discovered only on x-ray examination Although



Fig 4 Showing enlargement of submaxillary lymph nodes

cough or slight shortness of breath may have been present these symptoms rarely are marked unless the lungs are extensively affected and therefore occasion comparatively little comment

The intra-abdominal lymph nodes do not often increase to a size that can be detected by palpation They may at times compress the common bile duct and thus be responsible for jaundice and in rare instances as happened in an Italian boy in our series the mesenteric and

evidence of sarcoidosis of the lungs is detected sometimes by routine x ray examination Other patients even in the comparatively early stages do complain of cough usually without sputum and of shortness of breath in the later stages as the disease of the lungs progresses the respiratory symptoms become more serious and more numerous In general however the lack of correlation between the severity of symptoms and the extent and form of shadows in the roentgenogram is astounding and forms one of the remarkable features of the disease

Much the same incompatibility is noticeable between the physical signs and the appearance of the x ray film In the early stages the lungs may be clear to percussion and auscultation Later a few rales may be heard but usually the signs of patchy consolidation of emphysema or of solidification of large areas do not appear until disease of the lungs is far advanced

An explanation for the lack of symptoms and physical signs during the acute and early stages is to be found in the manner in which the sarcoid lesions are distributed through the lung Pathological examination shows that the miliary collections of epithelioid cells are deposited in the intersections of the interalveolar walls while the alveoli and bronchioles are entirely free of exudate (Fig 3)

Remission or healing is most likely to occur in those patients with what are thought to be early lesions but this may take place also when more pronounced changes are present It is impossible to predict however in any event that healing is permanent since exacerbations may be encountered months or years after all evidence of pulmonary involvement has disappeared

If on the other hand disease of the lung progresses a long train of symptoms may develop Extensive fibrosis of the pulmonary tissue may ensue with the production of emphysema and cyanosis followed by cardiac failure and death Partial or complete solidification of large areas of the lung is often accompanied by fever pain in the chest and loss of weight Cough is productive of sputum and hemoptysis has been recorded Secondary infections are not uncommon among which may be listed tuberculosis The pleurae may be infiltrated with sarcoid causing adhesions Very rarely an exudate of fluid accumulates in the pleural cavity which in some patients probably is the result of myocardial failure A combination of these conditions sometimes leads to death but at other times a regression of symptoms and signs occurs and quite extensive pulmonary lesions as depicted in the x ray film remain stationary for long periods of time

sarcoid and Schaumann lays considerable stress on the tonsils as a favorite seat of the disease Occasionally the diagnosis of sarcoid has been made from the pathological examination of tonsils removed at operation

Lungs

The routine use of the x ray for examination of the chest has disclosed the fact that sarcoidosis of the lungs is one of the commonest



Fig 6 Showing enlargement of mediastinal lymph nodes and reticulated shadows through lungs

manifestations of the disease Some form of intrathoracic involvement was found in 79 of our 90 cases and in at least 69 of these it could be determined that the lungs were affected during some stage of the disease Reisner[31] noted disease of the lung in 33 of his 35 cases and McCort and Wood[5] in 15 of their 26 patients although intrathoracic lymph adenopathy was present in all

A surprising matter concerning many of these patients is the complete absence of symptoms suggesting pulmonary disease The first



Fig 8 X ray of chest showing combination of filmy and nodular shadows

lobes (Fig 8) and fifthly dense masses occupying portions of one or more lobes (Fig 9)

Combinations of any of these pictures are seen and transformations from one type to another may take place after varying intervals of time Radiolucent areas that look like cavities are noted occasionally in con-

As a matter of fact most of our information concerning the distribution the extent the progress and the recession of the pulmonary changes comes from studies of roentgenograms made at different periods of the disease Several more or less distinctive types of shadows have been described and depicted [11, 31, 3, 51] The commonest finding is an enlargement of the hilar lymph nodes combined with shadows extending in streaks into the lung fields or with lacelike filmy shadows descending



Fig 7 Showing moderate enlargement of mediastinal and bronchial lymph nodes with shadows extending towards base and reticulated shadows in lower lobes

into the lower lobes (Fig 7), secondarily a striking bilateral enlargement of the hilar nodes with little or no involvement of the lung (Fig 5) thirdly a diffuse distribution of miliary shadows or denser small spots (Fig 101) fourthly diffuse filmy or nodular shadows in one or several



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nection with these denser shadows Some may be due to an associated active tuberculosis but in others tubercle bacilli are not found in the sputum and in one of our autopsies there was a smooth walled excavation from which tubercle bacilli could never be demonstrated

After a period of months or years a considerable reduction or complete disappearance of many of these shadows is not uncommon (Fig



FIG 9 Showing increase of root shadows extending into lungs

10b) King [3] states that in 23 of 37 of his patients the shadows in the lungs cleared completely or almost completely within 7 weeks to 3 years The miliary shadows are among those most likely to disappear Regression of

these was noted by Reisner[31] in 8 of 11 of his cases with complete resolution in 7 of these. Regression of the hilar node shadows takes place with nearly the same frequency but this may be followed by an extension of the pulmonary lesion.

Although the roentgenological pulmonary changes are of great significance, it is the belief of most radiologists that a diagnosis of sarcoid cannot be made from a study of the x ray film alone. The pulmonary shadows cast in erythema nodosum, rheumatic pneumonitis, eosinophilic



Fig 10 (a) X ray of chest showing extensive involvement of right lung and miliary shadows in left May 8 1940 (b) Same case one year later May 14 1941

infiltrations and histoplasmosis, any of which may resolve, or in silicosis, hyphomycoses, beryllium poison, miliary tuberculosis and carcinomatous metastases could all be confused with sarcoid.

Eye

The combination of lymph node enlargement, pulmonary sarcoidosis and ocular lesions is not uncommon, for it is rare to find that the eye is affected alone. Sarcoid of this organ or of its surrounding structures is

found according to Lindau and Lowegren[55], in over 15 per cent of cases but when a meticulous examination of the eye is made by a competent ophthalmologist, the incidence is much greater

The use of the slit lamp has proved of much value In 73 of our patients, who have been carefully examined 47 or over 64 per cent have shown unmistakable ocular lesions in one or another situation The commonest condition is a granular uveitis or iritis each of which occurred in 14 patients Keratitis, enlargement of the lachrymal glands or sarcoids of the eyelids, each was noted in 5 patients Hemorrhagic retinitis cataracts, glaucoma choreoretinitis conjunctivitis episcleritis (Fig 11) optic atrophy and optic neuritis were noted each occurring in one or two patients In two cases the type of lesion was not noted

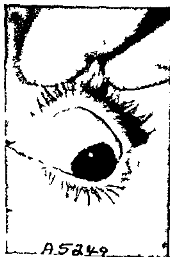


Fig 11 Sarcoid beneath scleral conjunctiva

Levitt[6] has called attention to the frequency with which sarcoid attacks the eye and has collected a huge bibliography on the subject, while Woods and Guyton state that sarcoid was the cause of uveitis in 15 of 102 patients suffering from this malady Much has been written about uveoparotid fever which forms one section of this chapter[1 13 8 59 5 60]

The eye may be involved early in the disease for many patients give a history of sore eyes or visual disturbances before any other manifestation of the disease becomes apparent As a rule both eyes are affected but to an unequal degree although sarcoid may be confined to one side There is usually some pain and lachrymation On examination small

granules may be seen on the lids in the conjunctiva over the sclera in the cornea or deposited about the margin of the iris producing indentations and irregularities The uveal tract appears granular In rare instances tiny granules are seen in the retina which may be the seat of hemorrhages in the choroid or in the optic nerve

The great importance of the ocular lesions lies in the fact that vision often is greatly impaired for the process may lead to glaucoma cataract or progresses until the eye is entirely destroyed Fortunately this does not always happen for healing may take place with only residual synechiae and without serious impairment of sight When the lachrymal glands are affected they enlarge perceptibly and have a finely granular appearance

Uveoparotid Fever

In uveoparotid fever the ocular lesions contribute one feature to a curious syndrome characterized in addition by swelling of the parotid glands facial palsies and often transient paralysis of other nerves The lachrymal glands frequently are enlarged Seven of our patients presented many of the symptoms and signs of uveoparotid fever

The syndrome is ushered in with fever malaise gastrointestinal disturbances weakness loss of weight and pains in the extremities Although the parotitis is not exquisitely painful it has been mistaken for mumps The bilateral uveitis occurs early and as the acute phase subsides other signs and symptoms make their appearance Paralysis of the facial nerve is present in about one third of the cases and in half of these it is bilateral Other cranial nerves may become involved such as the sensory branch of the fifth There may be partial ptosis strabismus or nerve deafness of the central type Dysphagia is fairly common and paralysis of the vocal cords causing hoarseness or of the soft palate has been described There may be evidences also of disturbance of some of the spinal nerves with sensory changes in the extremities loss of knee jerks or even weakness of an arm or a leg[69]

Uveoparotid fever progresses slowly with low fever to a subacute or chronic course lasting for weeks or months During this time other evidences of sarcoidosis are likely to arise Enlargement of the submaxillary cervical or supraclavicular lymph nodes is frequent cutaneous eruptions have been observed and roentgenograms have in some cases shown shadows developing in the mediastinum at the hilum or at the bases of the lung

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recorded[1 58 59] at autopsy Salveson[61] first drew attention to this possibility when he reported a case of sarcoidosis with heart block

During life attention usually is attracted to the heart by reason of its enlargement without signs of valvular disease or hypertension or on account of an unexplained irregularity in rhythm Symptoms and signs of myocardial failure usually are severe and progressive One of our patients who was ambulatory died suddenly on his doorstep At autopsy extensive infiltration of the myocardium by sarcoid was found (Fig 1) Abnormal rhythms are usual and furnish evidence of more or less serious injury to the myocardium Ventricular extrasystoles occurred in one of our patients and has been reported by Johnson and Jason[4] in combination with ventricular tachycardia Abnormalities in T waves occurred in another of our patients bundle branch block in one and complete heart block in still another (Fig 13) Auricular fibrillation has been observed The abnormal rhythms may alternate from one type to another

Infiltration of the myocardium is not the only cause of heart failure for this may result from widespread fibrosis of the lungs and be responsible for the death of the patient

Abdominal Organs

Spleen — The spleen is involved in a considerable proportion of cases of generalized sarcoid and occasionally is enlarged to so great a size that it dominates the clinical picture Friedman[63] states that the spleen was involved 21 times in 9 collected autopsies including one of his own Single epithelioid bodies scattered through the pulp is the usual finding (Fig 14) but large masses composed of agglomerated bodies are seen occasionally Evident enlargement during life is less common occurring in only 8 of Reisner's[31] 35 patients and in of our series of 90 patients In some instances however the spleen increases to a great size Splenomegaly was present in 3 colored women in our series in one of whom the organ was removed under the misapprehension that the patient had Banti's disease Similar mistakes have been reported[1 63] Usually the patient experiences only a sensation of heaviness and weight in the abdomen or complains of a lump in the side but gastric hemorrhage has been described in a few cases[63 64] and rupture of the spleen took place in one patient during an air raid in London

In the absence of ocular lesions swelling of the parotid, the lachrymal and submaxillary glands may simulate Mikulicz syndrome

Eventual recovery is the rule, unless the uveitis progresses to endanger the eyesight but death may occur usually from extension of the disease to other organs



Fig 12 Collection of epithelioid bodies infiltrating heart muscle

Heart

Localization of sarcoid in the lung and particularly in the eye is a serious matter for when the uveal tract the retina or the optic nerve is involved the consequences are apt to be grave Far less common but even more dangerous are the infiltrations of sarcoid through the pericardium or into the myocardium Several such instances have been

most often during the early stages and is rarely attended by symptoms of any kind, although jaundice has been described A very rare effect during the late stages is the development of a form of cirrhosis of the liver accompanied by ascites and fever One of our patients presented this clinical picture There was an elevation of alkaline phosphatase to 19 2 Bodansky units Biopsy of the liver made at exploratory operation showed fresh epithelioid bodies and portal cirrhosis Autopsy some



FIG 14 Showing collections of epithelioid bodies in spleen

months later disclosed advanced portal cirrhosis with fresh and healed sarcoids in the connective tissue

Gastrointestinal Tract

There has been active discussion regarding the relationship which sarcoid bears to some instances of regional ileitis and gastric granuloma

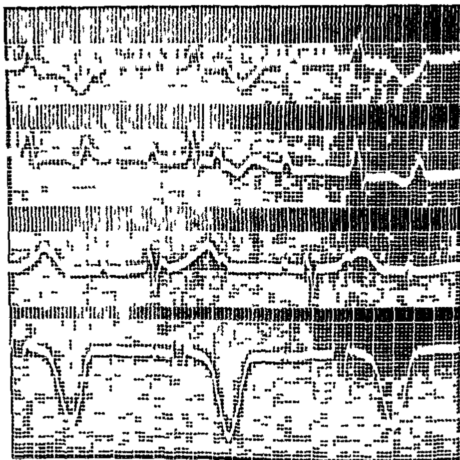


Fig 13 Electrocardiogram showing complete heart block with prolonged QRS and abnormal T waves

Liver - The liver also is quite a frequent seat of the disease showing nodules in 6 or one half of our autopsies and 17 times in Friedman's[65] 29 cases This is not detected in a great many patients during life for enlargement of the liver was observed in only 18 of our 90 patients and in only 6 of Reisner's[31] 35 cases Von Buchem[50] on the other hand obtained microscopical evidence of sarcoid in material extracted by liver puncture from 11 of his 14 cases and advocates this method as a valuable means of diagnosis

Basing their conclusions on the results of functional tests Harrell and Fisher[66] and Harrell[96] consider that the liver is quite frequently affected and was enlarged in 6 of their 11 cases Enlargement of the liver is noted

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Snapper concludes after thorough consideration that the two conditions are separate entities whereas Watson Rigler Wagenstein and Mc Carthy[6] report 2 cases which they believe typical histologically of sarcoid but after an exhaustive review of the literature and a search through their own material find only 6 others which they are willing to accept as instances of sarcoid Hadfield[68] on the other hand in an examination of tissue from 20 cases of regional ileitis describes changes in 13 resembling sarcoid so closely that he believes this disease is the cause of the majority of cases of ileitis The intestinal tract was not involved in any of our autopsies

Genitourinary System

The entire genitourinary system is susceptible to attack Isolated sparsely scattered epithelioid bodies in the kidney sometimes found at autopsy do not give rise to symptoms unless it possibly be albuminuria mentioned casually by a few writers Instances of severe forms of nephritis developing during the course of sarcoidosis have been recorded for Klinefelter and Salley[69] report one case and have found accounts of 3 others in the literature Klinefelter s patient was a young negro with generalized sarcoidosis who developed headache vertigo blurring of vision loss of weight fatigue dyspnea slight fever severe retinitis with retinal hemorrhages and exudates moderate anemia albuminuria cylindruria and renal insufficiency The blood pressure remained normal and the serum globulin was increased All symptoms improved remarkably under observation Only one of the recorded cases died[70] and at autopsy both sarcoid and tuberculous lesions were found in the kidney

Involvement of other portions of the urinary and genital tract are somewhat more frequent Sarcoid of the testicle epididymis and seminal vesicles has caused swelling pain and tenderness of these organs The prostate may be affected

In the female the uterus uterine mucosa and cervix may all be affected to such an extent that discharge and abnormal bleeding occur One of our negro patients who apparently had recovered from proven sarcoidal enlargement of the cervical and mediastinal lymph nodes with diffuse infiltration of the lungs complained of excessive uterine bleeding Curettage was performed and numerous epithelioid bodies typical of sarcoid were found in microscopic sections of the scrapings from the uterine mucosa

Integument and Locomotor System

Ever since Boeck's sarcoid was rescued from the limited field of dermatology the cutaneous lesions so elaborately reviewed at one time[16] have sunk into relative insignificance They do not by any means occur in a large proportion of patients for they are present in less than one half of the cases Only 14 of Reisner's[31] 35 patients and only 31 of our 71 patients whose skin was carefully examined had an eruption In some patients the lesions are numerous and produce a remarkable effect but in others they are so small and so scarce that a careful search over the entire body and particularly over the face shoulders back and arms has to be made in order to find them They never are seen alone for they form only one feature in the development of sarcoidosis They are accompanied regularly by enlargement of some lymph nodes are present occasionally in pulmonary involvement and are found usually when the bones are diseased as in lupus pernio

Boeck[3, 4] originally described 3 forms of eruption which appeared on the face the back and the arms but the lesions are not confined exclusively to these regions since they may be found over the legs abdomen or even on the skin of the penis

The first variety consists of small firm nodules of waxy or semi-translucent aspect with brown bluish or violaceous centres They are sharply demarcated and the surface is smooth and never shows ulceration (Fig 15) Individual lesions are widely separated but are often composed of a conglomeration of single tiny nodules giving the impression of a pitted surface They vary considerably in size ranging from a few millimeters to a centimeter or so in diameter They frequently heal leaving a flat shiny scar

The second variety consists of large nodules elevated above the surface sometimes extending into the subcutaneous tissues but having much the same general character as the first form

The third type which may be seen especially on the back and legs occurs as a flat infiltration extending over large areas of the skin The margins are sharply defined but are not elevated or indurated The surface is finely granular or at some stages is covered with shiny white scales which imparts a superficial resemblance to psoriasis Ulceration does not take place Healing is the rule As a result flat smooth scars remain that in the negro are pigmented

None of these eruptions is painful nor do they itch Consequently they may persist for weeks months or longer without undue disturbance

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somewhat reminiscent of tophi. Typical examples of lupus pernio are rather rare. Only 3 of our 90 cases presented this clinical syndrome in its full blown state.

Bones

Skeletal alterations without the complete clinical picture of lupus pernio are not uncommon, and the literature abounds in accounts of patients who exhibited this extraordinary feature of the disease. Jungling[1] gave an excellent description of 9 cases, many of which, however, were associated with lupus pernio. Changes in the bones were recognized in 9 of Reisner's[31] 35 patients, in 5 of Snapper and Pompen's 13 cases, in 6 of Kissmeyer's[11] 6 cases, in 6 of Harrell's[66] 11 cases, but in only 3 of Goeckerman's[1] 17 cases, and in 9 of 71 of our patients in whom the bones were carefully studied. As was pointed out by Schaumann, the actual incidence of osseous lesions may be much greater than is suggested by clinical examination, for even the x-ray may not define abnormalities in the bone marrow unless the disease is extensive or well advanced.

Comparatively few pathological studies have been made of the bones in these cases, but there is sufficient information to indicate that the earliest change consists in the scattered deposition of a few epithelioid bodies in the marrow spaces. When the sarcoids are numerous, they compress the cancellous bone and may enlarge the medullary cavity, so that the thin cortex bulges or is deformed. On healing they leave fibrous nodules of different sizes and shapes. The cortex itself is not invaded, nor are the joints implicated.

The favorite locations for these changes are the phalanges of the hands and feet, but they may be found in the metacarpal and metatarsal bones, sometimes in the long bones, rarely in the pelvis, and as a curiosity in the skull. Such a wide spread dissemination as occurred in one of Reisner's[31] patients must be most exceptional.

These patients at times experience pain in the affected extremities, but the lack of any great distress or interference with motion even in the advanced stages, when the deformities often become excessive, is astonishing.

In the earliest stages there is no evidence of disease of the skeleton in the physical examination. Later one of the first noticeable abnormalities is thickening of the shafts of the phalanges. The tips of the fingers are often squared, the nails flat, sometimes showing longitudinal stria

to the patient They are apt to increase slowly in size and, when they attain their maximum growth remain stationary for long periods

In the *lupus pernio of Besnier*, which is a unique type of sarcoid the cutaneous manifestations are associated with changes in the bones of the hands and feet This syndrome is characterized by swelling of the soft parts of the nose and nodular enlargements about the joints of the fingers and toes (Fig 16) The greatly enlarged bulbous nose presents a very



Fig 15 Showing eruption of sarcoid on face with swelling of nose such as occurs in "lupus pernio"

striking appearance for it projects as a brilliantly colored deep red or violet colored protruberance with a shiny or somewhat lumpy surface (Fig 15) The eyelids ears and cheeks also may show the more usual forms of eruption The nodules about the joints of the fingers and toes may be colored but more commonly they are pale or white being

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tions and the terminal phalanges are likely to be over extended (Fig 17) These changes make the hand look square and stubby As the process advances symmetrical white nodules may form about the inter phalangeal joints (Fig 16) These may be so numerous and so large that the hands in particular look like gnarled branches The fingers or toes are often deflected in one direction or another The tips of the fingers may grow small and pointed while the longitudinal striations deepen

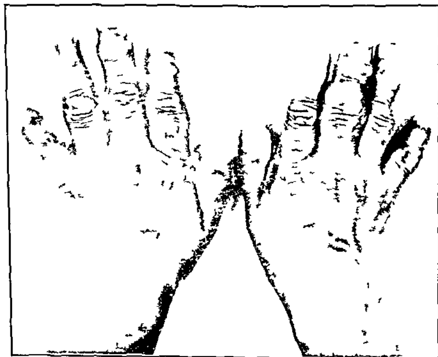


Fig 16 Showing appearance of hands in advanced stage of Lupus pernio

Still further progression often leads to mutilation with loss of one or another terminal phalanx In the most advanced phase the hands or feet become so swollen pudgy and deformed that they lose all semblance to human appendages

The roentgenological pictures are quite characteristic and are generally referred to as of two principle types These may occur together or in various stages of transition The first type is characterized by a diffuse lace-like filmy rarefaction of the medulla which may extend through a portion of the bone or along its entire length In places there

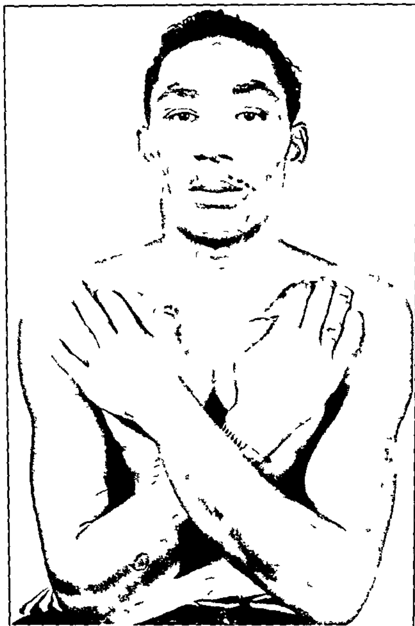


Fig 17 Hands showing slight enlargement of phalanges with squared fingers an stri tions of nails

are often spots or streaks of more pronounced rarefaction (Fig 18) In the second type the bones display punched out, radiolucent areas of different sizes and shapes In some instances only a very few, extremely small cystic areas of this sort are visible, in other cases when the process is advanced they are numerous large and responsible for distortion of the small bones partial disappearance of the terminal phalanges (Fig 19) or productive of huge holes in the larger bones

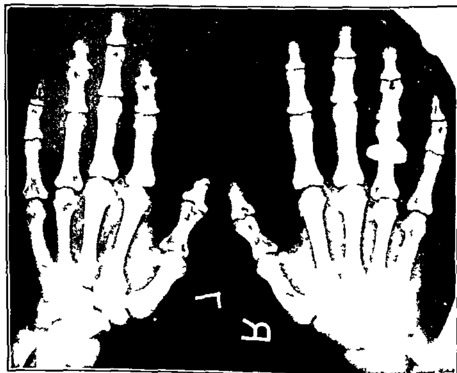


FIG 18 X rays of hands shown in Fig 17 Note density of phalanges and isolated areas of rarefaction

Pathological examination of the few cases on record demonstrate that the filmy rarefactions are connected with the seeding of fresh epithelioid bodies through the marrow while the clear spaces correspond to groups of fibrosed bodies that completely displace the cancellous bone

The process in the bones is liable to heal in any stage of its development and when it is arrested the deformities of the hands and feet may improve to some extent

Nodules of various sizes may be found in any of the voluntary muscles or about the tendons though these rarely give rise to any symptoms

Mucous Membranes and Other Tissues and Organs

As Boeck originally pointed out the mucous membrane of the nose is sometimes infiltrated with sarcoids under which circumstances the

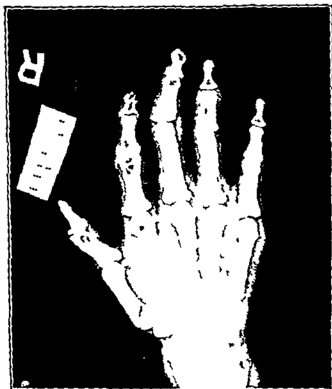


Fig 19 X ray of hands showing enlargement of phalanges meshlike rarefaction of medullary portions of phalangeal metacarpal and carpal bones and of radius and ulna Several isolated round areas of rarefaction are seen

nasal mucosa becomes granular or nodular The disease may extend to the nasopharynx and the paranasal sinuses involve the facial bones and penetrate through the cribriform plate to the base of the brain

In this manner the cerebral meninges have been implicated and according to Roos infiltrations at the base of the brain form one of the commonest sites for cerebral lesions in Boeck s sarcoid Under the circumstances invasion of the pituitary gland its stalk or the hypothalamus has occurred Diabetes insipidus has been observed in several patients[31] [3] Symptoms of diabetes mellitus were pronounced in one of our negro patients who had extensive involvement of the nasal mucosa and facial sinuses by sarcoid The disease was fatal At autopsy it was discovered that sarcoid had invaded the base of the brain, infiltrated the hypothalamus and completely replaced the pituitary gland and its stalk In at least one patient symptoms of pituitary atrophy or Simmonds disease have been associated with generalized sarcoidosis

Other symptoms and signs attributable to implication of the nervous system have been described Epileptiform convulsions lethargic states multiple polyneuritis spinal symptoms and meningitis have been recorded

Although the ubiquitous character of the disease has led to the discovery of solitary or scattered epithelioid bodies in almost every tissue and organ symptoms arising from their deposition in the thyroid para thyroids pancreas diaphragm and other unusual situations so far have not attracted attention during life

Constitutional Reactions

Considering the widespread dissemination of the lesions in generalized sarcoidosis their persistence and the extensive invasion that may take place in so many vital organs the sparcity of constitutional symptoms and bodily reactions are most striking This is particularly surprising when one compares this disease with other forms of granuloma such as Hodgkin s disease syphilis and tuberculosis

Fever is only likely to occur during two active phases of the disease first in the early stages and particularly with the onset of uveoparotid fever secondly in the latter stages and especially when the lungs are extensively invaded During the quiescent periods when the physical evidences of sarcoidosis are often well marked there is rarely any rise of temperature In 75 of our patients in which the temperature was recorded it was not above 99 F in 37 or almost one half In 8 the temperature varied between 101 2° and 102 F and in only 3 did it ever rise above 102 2 F

The usual form of fever during the active stage is an irregular elevation of temperature ranging between 99 - and 101 F This occurred in -7 of our patients In patients who have advanced pulmonary lesions the appearance of a persistent irregular fever may indicate the onset of caseous tuberculosis

Loss of weight and a feeling of fatigue are not uncommon in the acute stages and during exacerbations When the active phase subsides as it often does the weight and strength return to normal and in the quiescent periods are well maintained

Anemia is not a feature of the illness and the leucocyte count usually is within normal limits The differential count exhibits at times an increase in monocytes and a moderate eosinophilia is not unusual In 30 per cent of 60 of our cases there was an increase of eosinophiles above 4 per cent and in 7 of these the eosinophiles ranged from 11 to 1 per cent or higher

Other constitutional reactions manifest only by technical examinations are usual Among these is an elevation of the sedimentation rate which according to most recent writers accompanies not only the active stage but at times the supposedly quiescent stage In 36 of our patients the sedimentation rate was found to be elevated in 5 and in 17 of these the corrected figure lay between 0 and 40 mm

Another interesting reaction to the disease is the marked elevation of serum proteins that is likely to take place during the progressive phases Salvesen[81] first drew attention to this abnormality and since then his observation has been confirmed repeatedly Determinations of the serum proteins were made in 6 of our patients In 27 or almost one half the total serum protein ranged from 8 0 to 10 9 gm per 100 c c These abnormal increases in protein were due to an elevation of the globulin fraction which ranged from 4 0 to 6 9 gm per 100 c c in 8 of the cases Moreover the hyperglobulinemia was observed in some instances when the total serum proteins were not unduly high Electrophoretic analyses made in 1 of our cases by Fisher and Davis[4] demonstrated conclusively that the gamma globulins at the expense of the albumin fractions are responsible for these increases These abnormalities were found in the serum from patients who were in the active stage of the disease The sera from 4 patients without signs of activity proved to be almost normal Seibert and Nelson[7] who have estimated electrophoretically the serum proteins in several forms of chronic disease report conspicuous elevations of the gamma globulin in 6 case of sarcoid In tuberculosis on the other hand the conditions were different for when the disease was

moderately advanced an increase was found in the α_2 globulins, although slight elevations of the gamma globulins were sometimes detected in cases of minimal and active tuberculosis.

An increase in the calcium content of the serum has been recorded also[66] and is stated to reach figures as high as 16.8 mgm. per 100 c.c. in one patient with uveoparotid fever complicated by renal insufficiency, and 16.3 mgm. in another patient, who showed calcium deposits in the eye and in the spleen, kidneys and stomach discovered on x-ray examination.[6] Such a condition must be extremely rare and even noticeable elevations of serum calcium are unusual.[31, 77] Only 6 of 24 of our cases in which determinations of the serum calcium were made showed increases to 11 mgm. or more and the highest figure recorded was 16.5 mgm. per 100 c.c. This occurred in a patient who was in uremia with an elevation of non-protein nitrogen of the blood to 108 mgm. per 100 c.c. At autopsy renal calculi were found with extensive infection of the kidneys which were also infiltrated by masses of sarcoid. There was in addition hyperplasia of the parathyroid glands. In the remaining 5 instances the blood calcium was not increased above 12.7 mgm. per 100 c.c. It seems probable that the hypercalcemia is related in part at least to the hyperproteinemia.

There appears to be no significant alteration in the phosphorus content of the serum in Boeck's sarcoid. Abnormal amounts of alkaline phosphatase have been reported in the serum of some patients during the active stages of sarcoidosis[66] and is said to reach figures as high as 17.5 Bodansky units.[7] Although it is difficult to explain these increases in most instances, it seems probable that involvement of the liver might be responsible at times. In one of our patients proven at autopsy to have cirrhosis of the liver associated with extensive deposits of sarcoids in this organ the alkaline phosphatase activity of the serum reached 19.6 Bodansky units during life. In a second patient with unexplained jaundice the figure was 35 Bodansky units. In 3 of 12 other patients the blood serum contained from 6.9 to 7.6 Bodansky units and in 2 of these the liver was found to contain sarcoid at exploratory laparotomy. In the few examinations that have been recorded the acid phosphatase has not been altered.

It can be concluded that the constitutional reactions to sarcoidosis itself are most likely to occur during the active stage of the disease and in comparison to the extent and distribution of the lesions in many patients they are surprisingly unimpressive and produce few symptoms. The most serious results are occasioned by the anatomical destruction

of tissues and organs and not by an intoxication due to an invasion of the body by the etiological agent

PROGNOSIS

The progress of sarcoidosis is so irregular and so varied that it is difficult or impossible to make any accurate prediction as to its eventual outcome The course at best is usually a long one and although complete healing probably takes place in many or indeed in most cases an apparent recovery may be followed months or years later by a recrudescence producing a totally different train of symptoms and signs from those that characterized the onset

Not uncommonly the disease is initiated by an attack of uveitis This may subside with or without serious residual effects Some years later acute disseminated lesions may be found in the lungs accompanied by enlargement of the mediastinal lymph nodes These in turn may disappear only to give place after a quiescent period to disease of the bones or to an eruption over the skin The reverse may happen also In one of our patients the first evidence of sarcoidosis was a generalized enlargement of lymph nodes with swelling of the lachrymal glands He apparently recovered but returned several years later with multiple lesions over the skin and shadows at the roots of the lung These disappeared but after another lapse of a few years his hands became involved and showed fairly extensive changes by x ray Occasionally the abdominal organs are the first to attract attention In one of our patients an enormous enlargement of the spleen led to splenectomy on the assumption that the patient had Banti s disease It proved however that the splenomegaly was due to sarcoid A few years later she developed extensive sarcoidosis of the lungs complicated subsequently by caseous tuberculosis

Perhaps one of the commonest modes of onset or at least one of the most frequent lesions that is first discovered is one of the many forms of pulmonary involvement which is accompanied generally by an enlargement of one or another group of lymph nodes but almost any of the multiform features of the disease may occur alone be combined at one time or another or follow one another in unaccountable sequence

In order therefore to be certain that permanent recovery has taken place the individual patient must be watched for long periods of time Reisner[31] followed 8 of his patients for an average of 5 years Regres

sion of the lesions often with complete disappearance of all physical evidence of disease occurred in 9, a state of continued stationary chronicity was observed in 5, a constantly changing character of disease was noted in 5 and a continuous progression took place in 9 with death in 7 of these

Death is not often or perhaps is never due to intoxication from the granuloma itself Death when it is not the result of a secondary infection or some unrelated disease usually is caused by such an extensive invasion of one or another vital organ that its functions are fatally impaired Widespread progressive infiltration of the lung may cause death from secondary heart failure or a direct invasion of the myocardium itself may bring this about Tumor like formations in the meninges have caused convulsions and coma followed by death In a fair proportion of patients death is due to some intercurrent and unrelated disease

Rapidly progressive caseous tuberculosis has been responsible for a certain number of fatalities In 48 fatal cases of sarcoid collected from the literature 17 were found at autopsy to have tuberculosis of sufficient severity to account for death Of our 14 fatal cases 12 of which came to autopsy 3 were found to have died of acute or actively progressive tuberculosis In Reisner's series of 35 cases there were 7 deaths 5 of which were due to tuberculosis It cannot be doubted therefore that during some stage of the disease patients with sarcoidosis are prone to contract ordinary tuberculosis This is very likely to happen when the lesions of sarcoid are healing or have healed, at which time the reaction to tuberculin is converted from negative to strongly positive

A considerable number of patients have died from totally unrelated diseases and the lesions of sarcoid unsuspected during life, have been discovered only at autopsy This was true of 6 of our 12 cases that came to autopsy and has been the experience of others[47] Cancer hypertension accidental injuries epidemic meningitis and suicide have been among the immediate causes of exitus

Diagnosis

The ease or difficulty of suspecting or recognizing sarcoidosis clinically varies greatly The disease even though quite extensively distributed through the internal organs may produce relatively few symptoms or signs or it may present such striking features as for instance those of lupus pernio that it is almost unmistakable

The presence of any one of the types of cutaneous lesions should attract attention and requires a complete physical examination with x ray of the chest and hands as well as a careful ophthalmological survey. This procedure applies with equal force to patients who consult the ophthalmologist with granular uveitis or enlarged lachrymal glands. Inspection by means of the slit lamp may disclose in the iris or cornea the minute bodies typical of sarcoid while further explorations may show enlargement of superficial lymph nodes of hilar lymph nodes or of shadows in the parenchyma of the lungs. In the past there seems to be little doubt but that ocular sarcoid has been mistaken frequently for syphilis tuberculosis or iridocyclitis of unknown origin but at the present time ocular sarcoidosis has become so familiar that corroborative evidence of the disease is usually sought for when the etiology of the lesions in the eye cannot be established otherwise.

Very often the first evidence of sarcoidosis is discovered accidentally in an x ray film of the chest. The conformations and positions of the shadows may induce one to suspect that they are due to sarcoidosis and if in addition there is an enlargement of lymph nodes a cutaneous eruption or characteristic skelatal changes a diagnosis of sarcoid usually is justified. However it is generally conceded that the radiographic evidence is not alone sufficient to establish a conclusive diagnosis. Much the same patterns of shadows may be seen in the lungs in miliary tuberculosis and carcinoma metastases in silicosis and beryllium poisoning in mycotic disease in histoplasmosis in erythema nodosum in eosinophilic pneumonia and in several other infections.

Enlargement of the hilar and mediastinal nodes may occur also in tuberculosis and in any one of the forms of lymphoma. A definite conclusion can only be arrived at through accessory findings among which a histological examination of a lymph node of a lesion of the skin or of some other accessible lesion is of paramount importance.

When a localized or generalized enlargement of the superficial lymph nodes forms the outstanding feature sarcoidosis may be mistaken for Hodgkin's disease lymphosarcoma or one of the other forms of lymphoma. It may be confused with tuberculosis and infrequently with syphilis or metastatic carcinoma.

The skelatal changes resemble leprosy very closely and when the nasal mucosa also is affected the likeness becomes arresting it gave unjustifiable alarm in one of our patients. The alterations in the bones have been interpreted also as due to syphilis and to tuberculosis. The healed lesions or cysts might be suggestive of gout.

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Use of the Finsen light has been popular in Scandinavia while ultra violet light as well as x ray and radium have been employed in this country sometimes supposedly with apparent benefit Lomholt has reported favorable effects particularly upon the lesions of the mucous membranes, through intramuscular injections of antileprol which however had no influence on the lesions of the bones or internal organs

No success has followed the therapeutic use of tuberculin Marre has reported promising results from the treatment of lupus pernio and sarcoids of the skin with calciferol in doses of 50 000 to 100 000 units and Russell was impressed by the improvement of cutaneous lesions following the use of calciferol in one patient

Repeated exposures to Finsen light ultraviolet light or careful applications of x rays have been used within the last few years more generally than any other forms of therapy but whether the improvement reported by several observers was derived from the use of these rays or was spontaneous must remain for the present uncertain

Whatever form of treatment is selected it remains essential to institute those general measures of therapy that are found useful in the management of any chronic disease Rest is required when there is fever a high calorie diet particularly if there is loss of weight and fresh air and sunshine always

In the chronic inactive phases and during the quiescent periods the patient may be allowed up and about and usually can perform his normal activities There should always be interval examinations to determine whether the disease was progressing stationary or receding

BIBLIOGRAPHY

1 HUNTER F T Hutchinson Boeck s disease (generalized sarcoidosis) New Eng Jour Med 1936 CCXIV 346
PESNIER E Lupus pernio de la face Synovitis fungeuses (scrofulo tuberculeuses) symetriques des extremites superieures Ann de Dermat et Syph 1889 X 333
3 BOECK C Multiple benign sarcoid of skin Jour Cut and Genito urinary Dis 1899 XVII 543
4 BOECK C Fortgesetzte Untersuchungen uber das multiple benigne Sarcoid Arch f Dermat u Syph 1905 LXXIII 71 and 301 and Nochmals zur Klinik und zur Stellung des benignen Miliarlupoid Arch f Dermat u Syph (orig) 1916 CXXI 707

Great difficulties arise when the abdominal organs are affected without swelling of the superficial lymph nodes skin eruptions or skeletal changes Sarcoidosis of the spleen may cause so much enlargement of the organ that the condition is mistaken for Banti s disease or some other form of splenomegaly Many of the features of cirrhosis of the liver may be imitated by extensive sarcoidosis of that organ Instances of regional ileitis have been reported as due to sarcoid, but the relation between the two conditions is not clear

Failing all other evidences of sarcoid in these patients with abdominal involvement an exploratory laparotomy is justifiable and sometimes imperative but before resorting to such extreme measures, it is most important to explore every available region of the body in search of some indication of the disease elsewhere Not only in these cases of abdominal sarcoid but in any patient suspected of having the disease there should be a meticulous examination of the entire superficial lymphatic system in an effort to find at least one or two nodes that are even slightly enlarged It sometimes happens that a histological examination of one or two such lymph nodes shows a few or several typical fresh epithelioid bodies [8] When any of the superficial lymph nodes are perceptibly enlarged a biopsy always should be performed for the establishment of a conclusive diagnosis in a case suspected of sarcoidosis, this may allay anxiety on the part of the patient and the physician when some more serious condition has been considered as an alternative

Treatment

It is doubtful whether any of the numerous methods of therapy that have been used in Boeck s sarcoid have had a material influence upon the natural course of the disease Spontaneous recoveries and unexpected remissions are so frequent that the benefit derived from a single form of treatment is almost impossible to evaluate This is particularly true when the series of cases subjected to any type of therapy is necessarily limited by the comparatively small number of patients with sarcoid that come under the observation of any one physician

Arsenic has been employed for many years Fowler s solution in full doses is the preparation most widely recommended In a few instances rapid improvement is said to have followed the intravenous administration of arsphenamine or neoarsphenamine, but other patients have derived little or no benefit from them

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1 HUNTER F T Hutchinson Boeck s disease (generalized sarcoidosis) New Eng Jour Med 1936 CCXIV 346

BESNIER E Lupus pernio de la face Synovitis fongeuses (scrofulo tuberculeuses) symetriques des extremites superieures Ann de Dermat et Syph 1889 X 333

3 BOECK C Multiple benign sarcoid of skin Jour Cut and Genito urinary Dis 1899 XVII 543

4 BOECK C Fortgesetzte Untersuchungen uber das multiple benigne Sarcoid Arch f Dermat u Syph 1905 LXXIII 71 and 301 and Nochmals zur Klinik und zur Stellung des benignen Miliarlupoid Arch f Dermat u Syph (orig) 1916 CXXI 707

5 SNAPPER I and POMPEN A W M Pseudo Tuberculosis in Man Part I Besnier Boeck s Disease Visceral Localization of Sarcoids of Boeck De Erven F Bohn N V Haarlem 1938

6 BESANÇON F and LABBE M Maladie du systeme lymphatique Nouveau Traite de Medecine et de Therapeutique, 1911 XXV, 134

7 KIENBOCK R Zur Radiographischen Anatomie und Klinik der syphilitischen Knochenerkrankungen an Extremitaten Zeitschr f Heilkund (Chir) 190 XXIII 130

8 JUNGLING O Ostitis Tuberculosa Multiplex Cystica (eine eigenartige Form der Knochen Tuberkulose) Fortschrit a d Gebiete d Rontgenstrah 1919-21 XXVII 375

8a JUNGLING O Uber Ostitis Tuberculosa Multiplex cystoides zugleich ein Beitrag zur Lehre von den Tuberkuliden des Knochens Beitrag z klin Chirg 19 8 CXLIII 401

9 SCHAUMANN J Etude sur le lupus pernio et ses rapports avec les sarcoides cutanees Ann de Dermat et Syph 1917 V 1

10 SCHAUMANN J Sur le lupus pernio Memoire presente en Novembre 1914 a la Societe Française de Dermatologie et de Syphiligraphie pour le Prix Zambaco P A Norstedt et Soner Stockholm 1934

10a SCHAUMANN J Le lupus pernio et les sarcoids au point de vue etiologique Act Derm et Venerol 19 3 679

10b SCHAUMANN J Benign Lymphogranuloma and its cutaneous manifestations Brit Jour Dermat and Syph 19 4 XXXVI 515

10c SCHAUMANN J Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings Brit Jour Dermat and Syph 1936 XLVIII 399

10d SCHAUMANN J On the nature of certain peculiar corpuscles present in the tissue of lymphogranulomatosis benigna Act Med Scandinav 1941 CVI 39

11 KUZNITZKY E and BITTORF A Boecksches Sarkoid mit Beteiligung innerer Organe Munch med Wochenschr 1915 LXII 1349

12 HEERFORDT C F Ueber eine Febris uveo parotidea Subchronica an der Glandula parotis und der Uvea des Auges lokalisiert und haufig mit Paresen cerebrospinalen Nerven kompliciert Arch f Ophthalmol 1909 LXX 254

13 BRUINS SLOT W J Ziekte van Besnier Boeck en Febris Uveo parotidea (Heerfordt) Nederl Tijdsrft v Geneesk 1936 LXXX -859

13a BRUINS SLOT W J GOEDBLOED J and GOSLINGS J Die Besnier Boeck (Schaumann) sche Krankheit und die Uveo Parotitis (Heerfordt) Acta med Scandinav 1938 XCIV 74

13b LONGCOPE W T Sarcoidosis or Besnier Boeck Schaumann disease Jour Am Med Assoc 1941 CXVII 13 1

14 KISSMEYER A La Maladie de Boeck Sarcoides Cutanees Benignes Multiples Levin and Munksgaard Copenhagen 193

15 PAUTRIER L M Une Nouvelle Grande Reticulo endotheliose Maladie de Besnier Boeck Schaumann Masson & Cie Paris 1940

16 VOLK R Benignes Miliarlupoid (Boeck) Lupus pernio Tuberculose der Haut p 386 Handbuch der Haut und Geschlechtskrankheiten x/1 Jadassohn Berlin 1931

17 PINNER M Nonca eating tuberculosis Am Rev Tuberculoses 1938 XXXVII 690

18 MARTENSTEIN H Sarcoid Boeck und Lupus Pernio Arch f Dermat u Syph 19 4 CXLVII 70

19 HANNESSON H Besnier Boeck s disease review British Jour Tuberculosis 1941 XXXV 88

20 LEITNER St J Der Morbus Besnier Boeck Schaumann Chronische Epithelioidzellige Retikuloendotheliose sive Granulomatose Schwabe & Co Basel 1942

0a FREIMAN D G Sarcoidosis New Eng Jour Med 1948 CCXXXIX 664 709 743

1 REUNION DERMATOLOGIQUE DE STRASBOURG May 13 1934 Consacree a l etude de Sarcoides Bull d l Soc Franç de Dermat et de Syph 1934 XLI 00

LONGCOPE W T Some observations concerning the racial distribution and the arterial blood pressure in Hodgkin s disease Acta med Scandinav 1947 Supplement CXCVI 659

3 VON BUCHEM F S P On morbid conditions of the liver and the diagnosis of the disease of Besnier Boeck Schaumann Acta med Scandinav 1946 CXXIV 168

24 ROBINSON R C V and HAHN R D Sarcoidosis in siblings Arch Int Med 1947 LXXX 49

5 LOMHOLT S Douze cas de sarcoides de Boeck traites a l antilepro Bull de la Soc Franç de Dermat et de Syph 1934 XLI 1350

6 LONGCOPE W T and PIERSON J W Boeck s sarcoid (sarcoidosis) Bull Johns Hopkins Hosp 1937 LX 3

7 SCHAUMANN J and HALLBERG V Koch s bacilli manifested in the tissue of lymphogranulomatose benigna (Schaumann) by using Hallberg s staining method Acta med Scandinav 1941 CVII 499

8 FISHER J M Sarcoidosis the Chest and Heart Meyers J and McKinley C A Charles C Thomas 1948 Springfield Ill

9 HOLLISTER W F and HARRELL C T Generalized sarcoidosis of Boeck accompanied by tuberculosis and bacteremia Arch Path 1941 XXXI 1,8

5 SNAPPER I and POMPEN A W M Pseudo-Tuberculosis in Man Part I Besnier Boeck s Disease Visceral Localization of Sarcoids of Boeck De Erven F Bohn N V Haarlem 1938
6 BESANÇON F and LABBÉ M Maladie du systeme lymphatique Nouveau Traite de Medecine et de Therapeutique 1911 XXV 134
7 KIENBOCK R Zur Radiographischen Anatomie und Klinik der syphilitischen Knochenerkrankungen an Extremitaten Zeitschr f Heilkund (Chir) 190 XXIII 130
8 JÜNGLING O Ostitis Tuberculosa Multiplex Cystica (eine eigenartige Form der Knochen Tuberkulose) Fortschrit a d Gebiete d Rontgenstrah 1919 1 XXVII 375
8a JÜNGLING O Über Ostitis Tuberculosa Multiplex cystoides zugleich ein Beitrag zur Lehre von den Tuberkuliden des Knochens Beitrag z klin Chirg 19 8 CXLIII 401
9 SCHAUMANN J Etude sur le lupus pernio et ses rapports avec les sarcoides cutanees Ann de Dermat et Syph 1917 V 1
10 SCHAUMANN J Sur le lupus pernio Memoire presente en Novembre 1914 a la Societe Francaise de Dermatologie et de Syphiligraphie pour le Prix Zambaco P A Norstedt et Soner Stockholm 1934
10a SCHAUMANN J Le lupus pernio et les sarcoids au point de vue etiologique Act Derm et Venerol 19 3 679
10b SCHAUMANN J Benign Lymphogranuloma and its cutaneous manifestations Brit Jour Dermat and Syph 19 4 XXXVI 515
10c SCHAUMANN J Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings Brit Jour Dermat and Syph 1936 XLVIII 399
10d SCHAUMANN J On the nature of certain peculiar corpuscles present in the tissue of lymphogranulomatosis benigna Act Med Scandinav 1941 CVI 39
11 KUZNITZKY E and BITTORF A Boeckscher Sarkoid mit Beteiligung innerer Organe Munch med Wochenschr 1915 LXII 1349
12 HEERFORDT C F Ueber eine Febris uveo parotidea Subchronica an der Glandula parotis und der Uvea des Auges lokalisiert und haufig mit Paresen cerebrospinalen Nerven kompliciert Arch f Ophthalmol 1909 LXX 54
13 BRUINS SLOT W J Ziekte van Besnier Boeck en Febris Uveo parotidea (Heerfordt) Nederl Tigdsrft v Genuk 1936 LXXX 2859
13a BRUINS SLOT W J GOEDBLOED J and GOSLINGS J Die Besnier Boeck (Schaumann) sche Krankheit und die Uveo Parotitis (Heerfordt) Acta med Scandinav 1938 XCIV 74

47 NICKERSON A D Boeck s sarcoid report of six cases in which autopsies were done Arch Path 1937 XXIV 19
48 COTTER E F Boeck s sarcoid autopsy in a case with visceral lesions Arch Int Med 1939 LXIV 86
49 LONGCOPE W T and FISHER MURRAY A The effect of Schaumann s disease upon the heart and its mechanism Acta Med Scandinav 1941 CVIII 5 9
50 VON BUCHEM F S P On morbid conditions of the liver and the diagnosis of the disease of Besnier Boeck Schaumann Acta Med Scandinav 1946 CXXIV 168
50a SPINK W W Pathogenesis of Human Brucellosis with Respect to Prevention and Treatment Ann Int Med 1945 XXIX 38
50b GRIER R S NASH P and FREIMAN D G Skin Lesions in Persons Exposed to Beryllium Compounds J Indust Hyg and Toxic 1948 XXX 2 8
50c COAKLEY W A SHAPIRO R N and ROBERTSON G W Granuloma of the skin at the site of Injury by a Fluorescent Bulb Jour Am Med Assoc 1949 CXXXIX 1147
51 BRUCE T and WASSEN E Clinical observations of the course and prognosis of lymphogranulomatosis benigna Schaumann Acta Med Scandinav 1940 CIV 65
52 McCORT S S WOOD R H HAMILTON J B and EHRLICH D E Sarcoidosis a clinical and roentgenological study of twenty eight proven cases Arch Int Med 1947 LXXX 93
53 KING D S Sarcoid disease as revealed in chest roentgenograms Am Jour Roentgen and Rad Therap 1941 XLV 505
54 BERNSTEIN S S and SUSSMANN M L Thoracic manifestations of sarcoidosis Radiology 1945 XLIV 37
55 LINDAU A and LOWEGREN A Benign lymphogranuloma (Schaumann s disease) and the eye Acta Med Scandinav 1940 CV 4
56 LEVITT J M Boeck s sarcoid with ocular localization Arch Ophthalmol 1941 XXVI 358
57 WOODS A C and GUYTON J S Role of sarcoid and of brucellosis in uveitis Arch Ophthalmol 1944 XXXI 469
58 GARLAND H G and THOMPSON J G Uveo parotid tuberculosis Quart Jour Med 1933 II 157
59 WALDSTROM J Ueber gutartige universelle tuberkuloide Granulome mit besonderer Berucksichtigung der Uveo-Parotitis Zentralbl f d ges Tuberk Forsch 1936 XLV 4
60 LEVIN P M Neurological aspects of uveo-parotid fever Jour Nerv and Ment Dis 1935 LXXXI 176

30 LOMHOLT S Sur les lesions muqueuses dans les sarcoides Bull d la Soc Franç de Dermat et Syph (Reunion Dermatologique de Strasbourg) 1934 XLI 1142

31 REISNER D Boeck s sarcoid and systemic sarcoidosis (Besnier Boeck Schaumann disease) Am Review Tuberculosis 1944 XLIX 89 437

3 JADASSOHN W L'origine tuberculeuse de la maladie de Boeck Bull d la Soc Franç de Dermat et Syph 1934 XLI 1344

3 PINNER M WEISS M and COHEN A C Procutins and anticutins Yale Jour Biol Med 1943 XV, 459

33a LEITNER St J Neue Untersuchungen beim Morbus Besnier Boeck Schaumann (epithelioidzellige Granulomatose) Schweizer Zeitschrft f Tuberl 1946 III 108

34 DUBIN I N The poverty of the immunological mechanism in patients with Hodgkin s disease Ann Int Med 1947 XXVII 898

35 HAGN MEINCKE F Boeck s sarcoid and its relation to tuberculosis Acta Tuberculos Scand 1944 XVIII 1

36 SABIN F R DOAN C A and FORKNER C E Studies on tuberculosis Jour Exp Med 1930 LII Supplement No 3 1

37 KISSMEYER A and NIELSEN, J Notes sur l etiologie des sarcoides de Boeck Acta Dermat 1933 XIV 83

38 WILLIAMS R H and NICKERSON D A Skin reactions in sarcoid Proceed Soc Exp Biol and Med 1935 XXXIII 403

39 KVEIM A En ny og spesifik kutan reaksjon ved Boeck s Sarcoid Nord Med 1941 IX 169

40 DANBOLT N and NILSSEN R W Investigations on the course of Kveim s reaction and its clinical value Acta Dermato venereolog 1945 XXV 489

41 LOMHOLT S Beitrag zur Kveimreaktion bei Lymphogranulomatosis benigna Acta Dermato venereol 1945 XXIV 447

4 PUTKONEN T Über die intrakutan Reaktion von Kveim (KvR) bei Lymphogranulomatosis benigna Acta Dermato venereol 1943 XXIII Supplement X 1

43 HIGGINS H L Pulmonary sarcoidosis Conn State Med Jour 1947 XI 330

44 VAN ORDSTRAND H S HUGHES R DE NARDI J M and CARMODY M C Beryllium poisoning Jour Am Med Assoc 1945 CXXIX 1084

45 RUBIN E H and PINNER M Sarcoidosis one case report and literature review of autopsied cases Am Rev Tuberculosis 1944 XLIX 146

46 HOGAN C I Sarcoidosis a report of 5 cases with one autopsy Am Rev Tuberculosis 1946 LIV 166

78 PALMER J H Boeck s disease (sarcoid) its clinical groups and diagnosis Canad Med Assoc Jour 1940 XLIII 11
79 MARRE, J R Effect of calciferol on lupus vulgaris (two cases) lupus pernio and Boeck s sarcoid Proceed Roy Soc Med 1946 XL 10
80 RUSSELL B Sarcoidosis treated with calciferol Proceed Roy Soc Med 1946 XL 12

February 1 1950

61 SALVESEN H A The sarcoid of Boeck a disease of importance to internal medicine Acta med Scandinav 1940 CIV 1-3
6 JOHNSON J B and JASON R S Sarcoidosis of the heart Am Heart Jour 1944 XXVII 46
63 FRIEDMAN M Sarcoidosis of the spleen report of a case with autopsy and a study of intracellular 'asteroid bodies Am Jour Path 1944 XX 6 1
64 CHEVALLIER P and FIEHRER A Splenomegalie primitive Sarcoidique Sang 194 -43 XV 555
65 JAMES I and WILSON A J Spontaneous rupture of spleen in sarcoidosis Brit Jour Surgery 1945-46 XXXIII 80
66 HARRELL G T and FISHER S Blood chemical changes in Boeck s sarcoid with particular reference to protein calcium and phos phatase values Jour Clin Invest 1939 XVIII 687
66a HARRELL C T Generalized sarcoidosis of Boeck Arch Int Med 1940 LXV 1003
67 WATSON C J RIGLER L G WAGENSTEIN O H and McCARTHY J D Isolated sarcoidosis of the small intestine simu lating non specific ileojejunitis gastroenterol 1945 IV 30
68 HADFIELD G The primary histological lesion of regional ileitis Lancet 1939 II 773
69 KLINEFELTER H F and SALLEY S M Sarcoidosis simulating glomerular nephritis Bull Johns Hopkins Hosp 1946 LXXIX 333
70 HORTON B LINCOLN H S and PINNER M Noncaseating tuberculosis Am Rev Tuberculosis 1939 XXXIX 186
71 GOECKERMAN W H Sarcoids and related lesions Arch Dermat and Syph 19 8 XVIII 237
7 ROOS B Cerebral manifestations of lymphogranulomatosis benigna (Schaumann) and uveoparotid fever (Heerfordt) Acta med Scandinav 1940 CIV 1 3
73 TILLGREN J Diabetes insipidus as a symptom of Schaumann s dis ease Brit Jour Dermat 1935 XLVII 3
74 FISHER A M and DAVIS B D The serum proteins in sarcoid electrophoretic studies Bull Johns Hopkins Hosp 194 LXXI 364
75 SEIBERT F B and NELSON J W Electrophoresis of serum proteins in tuberculosis and other chronic diseases Am Jour Tuber culosis 1943 XLVII 66
76 SCHÜPBACH A and WERLEY M Hyperkalzaemia und organ Verkalkungen bei Boeckscher Krankheit Act med Scandinav 1943 CXV 401
77 STUART B M Sarcoidosis of Boeck metabolic study of 3 cases Am Jour Med Sci 1944 CCVIII 717

CHAPTER I–C

DISSEMINATE LUPUS ERYTHEMATOSUS AS A SYSTEMIC DISEASE

By HAMILTON MONTGOMERY

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INTRODUCTION

Lupus erythematosus is a chronic to acute disease of the skin. The disseminate types are associated with multiple varied systemic manifestations which become more marked and serious in proportion to the acuity of the disease. Acute disseminate lupus erythematosus, which was first described by Kaposi in 1872 as *erysipelas perstans faciei*[36] and later designated *erythema perstans faciei*[37] by Jadassohn, has been regarded by some authors as a separate disease from the chronic discoid type[2, ...]. However, cases in which there is a transition from a localized discoid to various disseminate types of lupus erythematosus are encountered frequently both clinically and pathologically. In our present state of knowledge diagnosis of lupus erythematosus is dependent chiefly on recognition of the cutaneous lesions[69]. One or more lesions presenting features of the discoid type usually can be demonstrated even in the most acute disseminate form. Classification of the types of lupus erythematosus and

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description of the cutaneous manifestations including histologic changes therefore are given before analyzing the systemic manifestations.

Very simple to complex classifications of lupus erythematosus are given in the literature.[64, 67, 3] I have followed the one adopted by O'Leary,[60] who divided lupus erythematosus into (1) the chronic discoid, (2) the generalized discoid or chronic disseminate, (3) the subacute disseminate and (4) the acute disseminate types.

This chapter is based on an analysis of 154 cases of disseminate lupus erythematosus out of a total of 480 cases of this disease seen at the Mayo Clinic. In 80 of the 154 cases the lupus erythematosus was of the chronic disseminate type, in 44 cases it was of the *subacute disseminate* type and in 30 cases it was of the acute disseminate type. Some of these cases have been reported previously.[27, 8, 44, 60] Postmortem studies were made in 15 of these cases; in 2 of the cases the disease was of the chronic disseminate type, in one of the cases it was of the subacute disseminate type and in 12 cases it was of the acute disseminate type. I acknowledge the use of data and unpublished studies by Rogin and O'Leary[63] and studies *of pathological changes in the kidney* by Stickney.[5] A thorough review of the voluminous literature has been made, but only a small portion of the references can be cited. The figures given in this paper are based on the group of cases studied at the Mayo Clinic and have been correlated with other studies in the literature.

Lupus erythematosus occurs most commonly among people living in the northern climate, but it may be found in any country or may affect any race. It is found frequently among Latin Americans[66] and among Negroes.[15] A familial incidence is a rare occurrence.[47] In cases of the disseminate form of the disease there is marked preponderance of women over men (Table I). Disseminate types may occur at any age; they have affected patients as young as *three months* and as *old* as seventy years.[14, 18, 5] However, the average age of the patients at the time of onset is less than it is in cases in which the disease is of the chronic discoid type. Dissemination from the localized discoid type may occur within a few months to as long as twenty-nine years after onset of the disease.

CUTANEOUS MANIFESTATIONS

Chronic Discoid Lupus Erythematosus

Chronic discoid lupus erythematosus occurs on the cheek and nose in the so-called butterfly distribution, but it may be seen as solitary, mul-

TABLE I

ANALYSIS OF 154 CASES OF DISSEMINATE LUPUS ERYTHEMATOSUS

Data	Type of disseminate lupus erythematosus		
	Chronic (80 cases)	Subacute (44 cases)	Acute (30 cases)
Women	61	80	77
Onset as discoid type	60	34	33
Average age at onset years	3	30	1
Average age at onset of dissemination years	39	38	8
Lesions of mucous membranes %	18	23	43
Prodromal symptoms %	5	27	33
Sensitivity to light %	2	3	23
Arthralgia or arthritis %	5	57	63
Fever	5	5	97
Anemia (less than 4 000 000 erythrocytes per cu mm of blood or 70% Hb) %	0	5	84
Leukopenia (less than 4 500 leukocytes per cu mm)	2	43	71
Falsely positive flocculation test or Wassermann reaction %	6	11	17
Renal irritation nephrosis or nephritis %	3	18	3
Infected tonsil %	68	54	40
Deaths attributable to the disease	8	4	100

Approximate Two patients are still living but both of them are critically ill in each instance the disease has been present for less than one year

tiple unilateral or bilateral plaques anywhere on the face scalp and ears and not infrequently on the lips especially the lower lip[n] The lesions consist of slightly indurated erythematous scaling plaques which vary from a few millimeters to many centimeters in diameter tend to clear in the center with atrophy and to spread peripherally There is an adherent silvery scaling associated with keratotic plugging of the orifices of the hair follicles and sweat ducts which in conjunction with the atrophy is diagnostic Varying degrees of telangiectasia and residual pigmentation are present Alopecia results when the lesions occur in the scalp Edematous tumid forms and bullous and telangectatic types are infrequent Constitutional manifestations are infrequent occasionally there is arthralgia leukopenia or evidence of renal irritation

Chronic Disseminate Lupus Erythematosus

Chronic disseminate lupus erythematosus is characterized by typical lesions of the discoid type on the thorax hands arms and back in addition to the lesions as described under the chronic discoid type The disease usually is the result of dissemination of the chronic discoid type Occasionally lesions may start elsewhere than on the face but in a few months

the face also is involved Erythematous multiforme like lesions and lichenoid and sarcoid like plaques are seen occasionally Constitutional symptoms are encountered not infrequently but usually are mild in character

Subacute and Acute Disseminate Lupus Erythematosus

Distinction between the subacute and the acute disseminate types of lupus erythematosus may be difficult at times and is made chiefly on

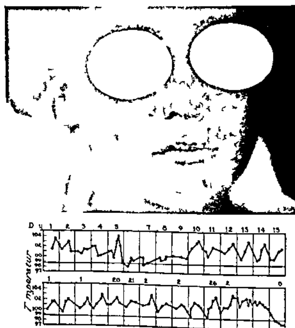


FIG 1 Acute disseminate lupus erythematosus (erythema facei perstans) associated with arthralgia lymphadenitis leukopenia albuminuria and septic type of fever The patient died at age of twenty one years of bronchopneumonia ten months after onset of the disease Necropsy revealed toxic hepatitis

the basis of the severity of the systemic symptoms and the acuity of the cutaneous lesions both of which are milder and tend to be more intermittent in character in the subacute type than they do in the acute type Both types of lesions may start as an erythema facei perstans (Fig 1) and may be confined to the face The dusky red hue of the plaques the sharp delineation of the borders and the varying degree of edema and induration are distinctive Cutaneous lesions often are limited to areas exposed to the light (Fig 2) and thus may simulate

pellagra. A toxic type of patchy to complete alopecia of the scalp, eyebrows and pubic region not infrequently occurs. Erythematous multiforme-like lesions are not uncommon, especially in the more acute types of the disease. The more acute the disease the more common and more severe are the lesions on the mucous membranes. Bullous and ulcerative lesions may occur on any mucous surface including that of the genitalia. In about 10 per cent of cases the lesions appear first on the neck, shoulders and hands, but within a few months the face also is involved. In the subacute type the clinical and histological picture may simulate that of



Fig. Subacute disseminate lupus erythematosus. One can note typical keratotic plugging. The patient had purpuric lesions on the hands and mouth, anemia, leukopenia, a septic type of fever and toxic nephrosis. Blood cultures were positive for streptococci.

lichen planus or in the involuting stages of the disease it may resemble that of poikiloderma atrophicans vasculare or idiopathic atrophy[6, 75]. Cutaneous lesions may involute spontaneously or as the result of treatment with resultant atrophy and a varying degree of pigmentation even to the extent of simulating Addison's disease[43]. Rarely cases are encountered in which exfoliative dermatitis is due to lupus erythematosus. Changes in the nails are infrequent and vary from simple paronychia to subungual hemorrhages and destruction of the nails.

The extent of the cutaneous lesions does not necessarily indicate the severity of the process If the cutaneous lesions have been present for more than a month one or more lesions of the discoid type usually can be demonstrated (Fig 3) When edema and one or more of the consti



Fig 3 Subacute disseminate lupus erythematosus showing characteristic follicular keratosis and also purpuric changes at the tips of the fingers Patient aged forty-eight years

tutional symptoms are present the prognosis becomes grave Regardless of whether the lesions were disseminate from the beginning of the disease or at first were of the chronic discoid type there was no difference in the duration or severity of the disease after the lesions became disseminate In 47 per cent of the cases in which the disease was of the subacute disseminate type the patients are known to have died as the result of lupus erythematosus In these cases the duration of the disease from the time the lesions became disseminate until death occurred varied from eight months to seven years the average was three years In the 30 cases of acute disseminate lupus erythematosus one patient was lost sight of 2 are still alive but have had disseminate lesions less than a year The remaining 27 patients are all dead death occurred from eight weeks

to a little more than two years after symptoms of acute dissemination had developed

Pathological Changes in the Skin

Histological studies of cutaneous lesions were made in 40 cases of the chronic discoid type and in 40 cases of the disseminate type of lupus erythematosus including 13 cases in which the disease was of the acute disseminate type. The histopathological picture usually is diagnostic if a specimen for biopsy is obtained from a lesion of several weeks duration and from a lesion that has not been subjected to irritating or stimulating preparations or to radiotherapy[19]. All transitions from chronic discoid to acute disseminate types were seen histologically (Fig. 4). This is contrary to the findings of some authors[19, 20].

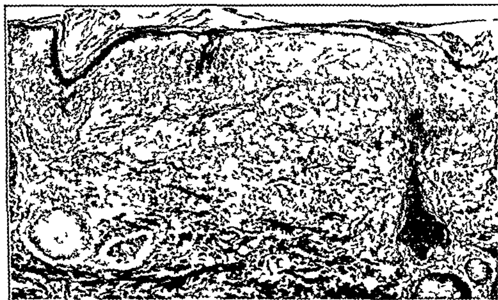


Fig. 4. Acute disseminate lupus erythematosus of six weeks duration. Histological features of both chronic discoid and acute disseminate types including keratotic plugging of hair follicles, atrophy of epidermis, liquefaction necrosis of basal-cell layer and dilatation of superficial vessels in the upper portion of the cutis (×4).

The earliest pathological changes in lupus erythematosus consist in dilatation of superficial blood vessels and lymphatics in the upper part of the cutis. Characteristic pathological changes, a combination of which permits a diagnosis of lupus erythematosus, consist of relative and abso

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each year for several years before the development of typical lesions of lupus erythematosus[60]

Dissemination of lupus erythematosus may occur after trauma or frostbite but not infrequently it follows exposure to sun or as the result of treatment with ultraviolet light (Table I) Photosensitization would seem to be a feature of the disease rather than its cause Contrary to the opinion expressed in recent articles[31] studies of the concentration of porphyrins in the urine by newer methods did not disclose any abnormality except in cases in which the disease was associated with fever It is known that the concentration of porphyrins in the urine usually is increased by various types of fever[6] Dissemination frequently follows the injudicious removal of teeth tonsils or other foci of infection It may occur following injection of neoarsphenamine various gold salts bismuth and tuberculin and it may occur in reactions to the oral administration of certain drugs such as the barbiturates and quinine and it may occur also at times following application of roentgen rays to lymph nodes

Systemic Manifestations

Systemic manifestations and constitutional symptoms of disseminate types of lupus erythematosus have been emphasized in recent articles in the literature[4, 41, 54, 58] Varying degrees of importance have been attached to various of these systemic manifestations[34, 57, 60, 9] In general the incidence of systemic manifestations increases with the acuity of the disease (Table I)

Arthralgia and Arthritis — Arthralgia and occasionally even true arthritis including the infectious polyarthritis with symptoms of rheumatic fever with or without effusions in the synovial membranes are encountered very frequently in cases of disseminate lupus erythematosus Multiple joints usually are affected Definite roentgenological changes have been reported

Fever — Transitory mild bouts of fever occasionally are encountered in cases of generalized disseminate lupus erythematosus In the subacute disseminate type fever which at first is slight and increases in the afternoon later may become septic in type The temperature may reach 103 F in the afternoon If the disease is of the acute disseminate type the temperature may even reach 105 F Fever usually is present in the subacute type and invariably is present at some time in the course of the acute disseminate type of lupus erythematosus During periods of remission the temperature may become normal or remain so for varying

lute hyperkeratosis (thickening of the corneous layer) keratotic plugging of hair follicles and sweat ducts and keratotic plugs independent of either preservation of the granular layer thickening of the prickle cell layer with adjacent regions of atrophy liquefaction necrosis of the basal cell layer, a perivascular chiefly lymphocytic infiltration about the dermal appendages dilatation of superficial capillaries and lymphatics, edematous changes in the cutis the presence of chromatophores laden with melanin pigment destruction of elastic tissue where the infiltration occurs and the absence of proliferative or obliterative changes in the walls of the deeper blood vessels In disseminate types dilatation of the superficial vessels and edema of the cutis atrophy of the epidermis and liquefaction necrosis of the basal cell layer are more prominent and the infiltration is less marked Sebaceous glands and hair follicles may be atrophied or absent Basophilic degeneration and swelling of elastic and connective tissue fibers are found only in specimens which are taken from a region exposed to light These changes occur in many other conditions and therefore are without diagnostic significance

In all types of lupus erythematosus there is a slight but definite increase in the number of Gitterfasern (lattice fibers) which suggests involvement of the reticulo endothelial system Edema and swelling of the endothelial cells in the superficial capillaries and lymphatics were seen frequently but true proliferative or obliterative changes were seen only in those cases in which the patients had been subjected to intensive *local radiotherapy*

Histological evidence of tuberculosis was found in two cases in which both sarcoid and lupus erythematosus were associated and confirmed by subsequent response to treatment Histologically lupus erythematosus at times may be difficult to distinguish from senile keratosis leukoplakia lichen planus and poikiloderma All of these conditions show liquefaction necrosis of the basal layer but usually they can be distinguished by concomitant findings

PRODROMAL SYMPTOMS AND FACTORS CAUSING DISSEMINATION

Prodromal symptoms such as arthralgia malaise and fatigue transitory bouts of fever and transitory infections as well as other systemic manifestations which will be mentioned later may precede the onset of cutaneous lesions of lupus erythematosus by several months to even several years *In* several cases of the subacute and acute disseminate types recurrent attacks of transitory erythema which occurred on the face and elsewhere on the body and lasted a few days or weeks recurred

cases in which necropsy was *performed* Stickney *found one case* of acute nephritis one of early chronic diffuse nephritis one of nephrosis and only one case of chronic glomerular nephritis Stickney found an increase in the number of endothelial cells in the glomerular tufts in 7 of the 15 cases and hyaline thickening of the capillary walls in 5 of the 15 cases Some thickening of the basement membrane was seen in several cases but the wire loop type of lesion as described by Baehr Klemperer and Schifrin was found in only one case Obliterative changes were not seen in arterioles or in the larger blood vessels Acute terminal infarcts were seen in the kidney spleen and liver in several cases but were not regarded as of etiological significance The renal changes did not seem specific for lupus erythematosus but suggested a toxic process The changes were similar to those described as occurring in the kidneys in cases of eclampsia[15] and occasionally in infectious diseases of long standing[3] Baehr and others emphasized the frequency of pathological changes in the kidney including the presence of wire-loop lesions and hyaline thrombi and that obliterative changes are found in the smaller blood vessels in various organs in the body as well as in the skin Rose and Pillsbury[60] found hypertension to be present in more than a third of their series of cases of lupus erythematosus in which lesions of the kidney were encountered Chronic glomerular nephritis has been reported in cases in which the patients are young persons[63, 6] In all except one of the cases in this series only older patients who had evidence of arteriosclerosis had evidence of hypertension Glomerulitis pyelonephritis hemorrhagic nephritis and chronic interstitial nephritis also have been described in association with disseminate lupus erythematosus[56, 71] Martenstein and Grunzow Irrgang[55] emphasized the frequent occurrence of arteriosclerotic changes in the aorta and Jlinsky[45] found an increase in concentration of cholesterol in the plasma and linked this with the arteriosclerotic changes in the vessels

Ocular Findings — A great many different types of ocular changes have been reported Tuberculous choroiditis a frequent and even dominant finding in a series of cases reported in Germany[46, 65] has not been described in any series of cases reported in this country Baehr Klemperer and Schifrin emphasized the occurrence of changes including vascular hemorrhages fluffy exudates and circumpapillary edema in the fundus in about half of their cases of disseminate lupus erythematosus Even choked disks bilateral albuminuric retinitis[6] eczematous retinitis and nontuberculous choroiditis have been reported[69] In this series of cases ocular findings were infrequent cotton wool exudates occurred in two cases and evidence of hypertension conjunctivitis chorioretinitis

periods. A persistent hyperpyrexia with a septic type of fever resembling that seen in typhoid fever and malaria but without as regular a rise and drop in temperature offers a serious prognosis.

Changes in the Blood. — In the 154 cases the findings regarding anemia and leukopenia corresponded to those reported in the literature (Table I). The persistence of leukopenia in the face of a septic type of fever usually is indicative of a fatal outcome. A leukocyte count as low as 1 400 to 2 000 per cu. mm. of blood is not unusual. There usually is a relative increase in lymphocytes at times in the leukocytes[83]. Thrombocytopenic purpura may precede, accompany or follow the onset of the disseminate type of lupus erythematosus[40, 5]. Purpuric and hemorrhagic lesions, however, are seen frequently without abnormalities in the platelet count[18, 40, 5]. In this series of cases other changes in the blood were seen: aplastic anemia, hemolytic icterus, pernicious anemia and myeloid immaturity, each was encountered in one case. An increase in monocytes has been reported frequently[57] and leukemic changes have been described[16]. There frequently is a marked elevation in sedimentation rate; in one of the 154 cases a reading of 164 mm. per hour was obtained.

A striking feature in this series of cases, which emphasizes the toxic changes that occur in the blood, was that the percentage of falsely positive results of serologic tests for syphilis increased according to the acuity of the disease (Table I). In cases in which the disease was of the chronic disseminate type, the results of the Kahn and the Kline test might be 1 plus or 2 plus, while the results of the Hinton test and the Wassermann (Kolmer's modification) reaction might be negative. In cases of the subacute and acute disseminate types of the disease it was not uncommon to find that the results of three or four serological tests were positive in varying degrees and in two cases the results of all four tests were repeatedly 3 plus or 4 plus, although there was no other evidence to warrant a diagnosis of syphilis. These findings are supported by those of Jlinsky[35] but not by those of Poehlmann[65].

Diseases of the Kidney. — In a great many reported cases in which nephritis has been associated with disseminate types of lupus erythematosus the diagnosis apparently was based on the presence of albumin, erythrocytes and a few casts in the urine. Adequate studies of renal function have been made in a relatively small percentage of such cases. A decrease in renal function and azotemia usually occurs only in the terminal stages of the disease[75]. The percentage figures given in Table I are based on the number of cases which had persistent and marked albuminuria and cylindruria without evidence of disturbance in renal function and on evidence of nephrosis or true nephritis. In the 15

cases in which necropsy was performed Stickney found one case of acute nephritis one of early chronic diffuse nephritis one of nephrosis and only one case of chronic glomerular nephritis Stickney found an increase in the number of endothelial cells in the glomerular tufts in 7 of the 15 cases and hyaline thickening of the capillary walls in 5 of the 15 cases Some thickening of the basement membrane was seen in several cases but the wire loop type of lesion as described by Baehr Klemperer and Schifrin was found in only one case *Obliterative changes were not seen in arterioles or in the larger blood vessels* Acute terminal infarcts were seen in the kidney spleen and liver in several cases but were not regarded as of etiological significance The renal changes did not seem specific for lupus erythematosus but suggested a toxic process The changes were similar to those described as occurring in the kidneys in cases of eclampsia[4] and occasionally in infectious diseases of long standing[5] Baehr and others emphasized the frequency of pathological changes in the kidney including the presence of wire loop lesions and hyaline thrombi and that *obliterative changes are found in the smaller blood vessels in various organs in the body as well as in the skin* Rose and Pillsbury[60] found hypertension to be present in more than a third of their series of cases of lupus erythematosus in which lesions of the kidney were encountered Chronic glomerular nephritis has been reported in cases in which the patients are young persons[57 4] In all except one of the cases in this series only older patients who had evidence of arteriosclerosis had evidence of hypertension *Glomerulitis pyelonephritis hemorrhagic nephritis and chronic interstitial nephritis also have been described in association with disseminate lupus erythematosus*[66 14] Martenstein and Granzow Irrgang[5] emphasized the frequent occurrence of arteriosclerotic changes in the aorta and Jlinsky[4] found an increase in concentration of cholesterol in the plasma and linked this with the arteriosclerotic changes in the vessels

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choroidal degeneration plugging of the disks and nephritic angiospasm occurred in one case each Hemorrhages are not uncommon in the terminal stages of the disease In many cases in which there was evidence of renal irritation there was no evidence of ocular changes

Diseases of the Heart — Cardiac murmurs of various types are encountered commonly in disseminate types of lupus erythematosus without significant pathological changes being demonstrable at necropsy In several cases the patients had had rheumatic heart disease since early childhood A diagnosis of bacterial endocarditis was made in 6 or 20 per cent of the cases of acute disseminate lupus erythematosus and in one case of the subacute disseminate type Necropsy revealed bacterial endocarditis in 3 of 12 cases of the acute disseminate type and pericarditis in 3 other cases Aschoff s bodies were present and bacteria were demonstrated by staining methods and by blood culture These findings are directly opposed to those of Baehr Klemperer and Schifrin In none of the 154 cases were the requirements of the Libman Sacks syndrome[48] of nonbacterial verrucous type of endocarditis fulfilled yet in many of their cases the patients had typical cutaneous lesions of acute disseminate lupus erythematosus

Disease of the Liver and Spleen — Kaposi[36] found fatty and amyloid changes in the liver in cases of disseminate lupus erythematosus Cirrhosis has been associated with alcoholism in some cases of lupus erythematosus[3] and jaundice was present in a number of reported cases[50] In one of the 154 cases the patient had an atypical type of hemolytic icterus and another patient had simple jaundice In 4 cases definite hypertrophy of the liver was found at necropsy Histological examination disclosed a moderate to severe degree of necrosis leukocytic infiltration and at times fatty degeneration about the central veins but there was no evidence of passive congestion As in the kidney the changes were essentially toxic in nature and were similar to those seen in cases of eclampsia Other authors have found fatty changes[50] [6] abscesses and swelling and terminal infarcts sometimes have been encountered[33] Rose and Pillsbury[63] emphasized the frequent occurrence of splenitis and splenomegaly and clinical evidence of splenic infarction in cases of acute disseminate lupus erythematosus Moderate splenomegaly was present in several of the 154 cases

Disease of the Brain — Keil[41] suggested that the cerebral system often bears the brunt of the attack in cases of lupus erythematosus Kaposi noted atrophy of cortical substance edema of meninges and acute hydrocephalus in two cases Involvement of the gasserian ganglion has been reported[60] In one of this series of cases the patient died of meningitis

following acute tonsillitis and otitis media Infarcts of the left hypocampus occurred in another case in which the patient had generalized arteriosclerosis

Gastrointestinal Symptoms —Goeckerman[77] and Madden[84] have emphasized the occurrence of gastro intestinal symptoms in disseminate types of lupus erythematosus At times these symptoms have resulted in unnecessary operations Generalized or localized abdominal pain and other symptoms have led to a diagnosis of cholecystitis appendicitis ulcer and colitis Any of these conditions however may be present In one case in this series the patient had ulcerating tuberculous colitis ileitis and terminal peritonitis associated with a septic type of fever and a leukopenia which taken together suggested a diagnosis of typhoid fever Abdominal crises similar to those which Osler[63] noted in the erythema group of diseases may be encountered Pathological changes in the pancreas are encountered very rarely

Disease of the Lungs and Pleura —In cases of lupus erythematosus death usually results from bronchopneumonia but it occasionally is caused by lobar pneumonia Pleurisy with effusion pericarditis and pulmonary abscesses not infrequently have been reported as terminal manifestations of the disease

Foci of Infection —Foci of infection play a prominent role in disseminate types of lupus erythematosus and exacerbation of a focus of infection may be followed by dissemination or even by death Evidence of tonsillar or dental sepsis occurs more frequently however in the chronic disseminate than it does in the acute disseminate types Prostatitis cholecystitis and appendicitis were encountered not infrequently A focus of infection probably acts indirectly by lowering the resistance of the patient to the lupus erythematosus

Libman Sacks Syndrome

In 1924 Libman and Sacks under the title of a hitherto undescribed form of valvular and mural endocarditis reported a group of cases in which the patients had fever white-centered petechiae in the skin and evidence of disease of the kidney Blood cultures were repeatedly negative and in contrast to rheumatic endocarditis Aschoff s bodies were not demonstrable in the heart Subsequent cases have been reported by Baehr Klemperer and Schifrin as a diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis The syndrome has come to include the presence of fever leukopenia petechiae purpura embolic phenomena evidence

of endocarditis pericarditis renal injury arthritis pleural effusion and persistently negative blood cultures[31, 41, 69] Many of these symptoms already have been discussed earlier in this chapter

The Libman Sacks syndrome has been regarded respectively as a separate entity as related to the Osler erythema group because of the purpuric manifestations and finally as acute disseminate lupus erythematosus[5, 39] All these points of view are in a sense correct and in many cases of Libman Sacks syndrome the patients have had all the cutaneous and systemic manifestations of acute disseminate lupus erythematosus In other cases however cutaneous symptoms have been absent or they have appeared as transitory erythema and purpura which lacked the clinical and histological features of lupus erythematosus[5, 41, 69] A nonbacterial endocarditis and petechia purpura and embolic phenomena are not predominate symptoms of subacute or acute disseminate lupus erythematosus nor is their presence necessary for diagnosis In some of the cases otherwise similar to those with the endocarditis no vegetations were present in the heart these it would seem should be grouped in the same category as the other patients The same thing may be said too of other variations from the typical case Probably a better understanding of this group eventually will come after study and analysis of many more patients have been made

Etiology

The term lupus erythematosus is unfortunate as the cause of the disease remains to be determined and the condition is entirely distinct from lupus vulgaris which is a form of cutaneous tuberculosis Jadassohn[3, 33] always has maintained that there are multiple and varied etiological factors in contrast to the tendency of French[13, 64] German[46, 6] and Viennese[70] schools who support the theory that the disease is tuberculous in origin Keil[33] emphasized that postmortem evidence of active or possibly active tuberculosis was available in only 20 per cent of 125 cases reported in the literature Lymphadenopathy has been diagnosed as tuberculous when caseation was the only pathological change that was found Demonstration of *Mycobacterium tuberculosis* by animal inoculation with material obtained from a plaque of lupus erythematosus has been reported in two or three cases[11, 77] The specificity of tuberculin tests Much s granules and Landouzy s conception that a typho bacillus was the cause have not stood the test of time Tuberculotoxins and modified nonacid forms of *Mycobacterium tuberculosis* have been suggested by French authors[13, 64] to explain the absence of pathological changes

of tuberculosis in the cutaneous lesions of lupus erythematosus. Cases in which acute disseminate lupus erythematosus is associated with active tuberculosis are still being reported[11] but in most series of cases of lupus erythematosus the incidence of tuberculosis is no greater than for any nontuberculous cutaneous disease.[6, 14, 33] In less than 8 per cent of the 154 cases in this series the lupus erythematosus was associated with various types of cutaneous tuberculids. A familial history of tuberculosis was obtained in 20 per cent of the cases. In 10 per cent of the cases in which the disease was of the acute disseminate type examination disclosed an adenopathy which was suspected clinically or pathologically of being tuberculous. Clinical or postmortem evidence of active tuberculosis was obtained in two cases of the generalized disseminate type, in one case of the subacute disseminate type and in two cases of acute disseminate lupus erythematosus. In terms of postmortem findings active tuberculosis was present in 2 of 15 cases and healed tuberculosis was found in 4 cases. The tuberculous origin of disseminate lupus erythematosus remains to be proved, although activation of a tuberculous focus may contribute to dissemination of the disease and may even result in death.

A streptococcic origin was emphasized first by Barber[3, 4] and since then many cases have been reported in which streptococci played a prominent[50, 56, 71] etiological role. Against this conception there is only a small percentage of cases in which positive blood cultures have been obtained. This was true in this series of cases. Nonhemolytic streptococcus was demonstrated in the blood culture in one case in which the subacute disseminate type of the disease was associated with endocarditis. *Streptococcus viridans* was found in two cases, and staphylococcus was found in the blood stream in one case in which the disease was of the acute disseminate type, and streptococci and pneumococci were found in one case and pneumococci in two cases shortly before death. Welsh[77] in a study of the specificity of streptococci in different diseases obtained positive cultures from the blood or in smears from the nasopharynx and positive results with serum potential studies in 3 of 4 cases of the chronic disseminate type, in 7 of 8 cases of the subacute disseminate type and in 4 cases of the acute disseminate type. He obtained positive results in 2 of 6 cases of the chronic discoid type. This work needs confirmation.

Gennerich[43] expressed the opinion that the lymph nodes are involved in the disease as a result of certain ferments of lymphocytes which have a special affinity for the vascular system and account for the subsequent reaction in the skin to light, air and mechanical agents. Schauman compared lupus erythematosus to lymphogranulomatosis benigna (sarcoidosis) on the basis of common involvement of the reticulo-endothelial

system and Galowoski[21] would support this conception. Baehr and others and also Keil[41] emphasized the involvement and the obliterative changes in the small blood vessels in the skin and other organs and the occasional occurrence of thrombosis of the veins and the association of periarteritis nodosa[8, 34, 4] and thrombocytopenic purpura[40, 57] with disseminate lupus erythematosus. In two cases in this series there was thrombosis of the peripheral veins and in one case there was evidence of Raynaud's disease. My histopathological studies do not substantiate this conception of lupus erythematosus as a vascular disease[13, 41] except that the capillaries were dilated and their walls edematous both in the skin and internal organs.

The preponderance of acute disseminate lupus erythematosus among women has been attributed to ovarian dysfunction and to pregnancy[46]. In 4 of the 154 cases dissemination occurred during pregnancy or at its termination. Abnormalities in the pelvic organs that might be regarded as of etiological significance have not been reported. In 3 cases disseminate lupus erythematosus was associated with hyperthyroidism and in one of these cases the lesions involuted following thyroidectomy. Lewis emphasized[41, 43] that lesions of lupus erythematosus affected regions of skin supplied by the atonic vessels and Keil associated this with the more pronounced blushing reflex in women. Many other etiological factors have been suggested; these include a nervous fatigue factor among young women,[1] hereditary syphilis[64] and the frequent incidence of lead[51] in the skin. An important role has been attributed to allergic[1] factors.

Differential Diagnosis

A diagnosis of chronic disseminate and subacute disseminate lupus erythematosus usually is easily made clinically on the basis of demonstration of one or more lesions of the chronic discoid type. When in doubt the removal of a specimen of skin for biopsy may establish the diagnosis. Erythema faciei perstans is distinctive from the more acute lesions of erysipelas and from the transitory lesions of erythema multiforme. Many authors emphasize the close relationship between lupus erythematosus and erythema multiforme[7, 81] and in a few cases erythema multiforme has been diagnosed erroneously as acute disseminate lupus erythematosus. The same is true of transitory erythema resulting from sensitivity to light and toxic erythema caused by treatment with gold and actinic rays. In the latter instances a period of observation may be necessary to determine whether true dissemination has occurred or whether the erythema is simply transitory. These types of erythema may be distinguished, however, on the basis of concomitant findings. The same is true of lichen

parities, pellagra, pernio, Raynaud's disease and various types of cutaneous tuberculosis associated with lupus erythematosus. The Osler erythema group has been ascribed by some authors to lupus erythematosus and by others to the Libman-Sacks syndrome, but in only two or possibly three of Osler's cases could, I believe, the lesions be regarded as disseminate lupus erythematosus. Cases of transient erythema of the face have been reported as cases of acute disseminate lupus erythematosus or as cases of Libman-Sacks syndrome when most likely they were cases of a prodromal type of erythema and did not present clinical and histologic features of lupus erythematosus. Diagnosis of disseminate lupus erythematosus based on lesions limited to the hands or trunk and without involvement of the face I believe is most hazardous without histopathological confirmation. Mention need only be made of the rheumatic erythema, mentioned by Keil, in relationship to rheumatic heart disease. Dermatomyositis may simulate acute or subacute disseminate lupus erythematosus closely in distribution to light-sensitive regions and may be associated with arthralgia and myalgia. The pathological picture of dermatomyositis is different from that of lupus erythematosus. Cases in which the disease has been regarded as dermatomyositis associated with lupus erythematosus have, however, been reported. The so-called Senear-Usher syndrome has been regarded as a bullous type of lupus erythematosus or as a relatively benign form of pemphigus (pemphigus erythematodes, Ormsby) or finally as a separate entity. At different stages there may be lesions resembling those of seborrheic dermatitis, erythema multiforme, pemphigus and lupus erythematosus. The condition differs from the disseminate types of lupus erythematosus in the relative freedom from constitutional illness and a tendency toward chronicity. The histopathological changes apparently do not fit in with either lupus erythematosus or pemphigus.

Treatment

The most important treatment for subacute and acute disseminate types of lupus erythematosus is rest in bed, good nursing care and measures to build up the patient's general resistance. Repeated transfusions and the use of bone marrow, the sodium salts of the pentose nucleotides from the ribonucleic acid of yeast (pentnucleotide), a synthetic preparation of quinoline (plasmochin) and preparations of iron are valuable in combating the anemia and leukopenia. The avoidance of sunlight, even of that coming through the window pane, is important. Local soothing applications such as wet dressings of aluminum subacetate

calamine lotion boricated cold cream 3 per cent ichthyol in an ointment of zinc oxide may be used Unless the patient is found sensitive to quinine the use of this drug especially in the form of quinine bisulfite by mouth[1] frequently results in temporary and occasionally in permanent improvement Intolerance to the drug may develop at any time

Removal of foci of infection should be attempted only after cutaneous and systemic manifestations have become quiescent a good working rule is to remove only one tooth at a time Fatal dissemination frequently results from the injudicious removal of foci of infection but proper and cautious removal may result in involution and at times even in a cure in some of the cases of disseminate lupus erythematosus

In 1923 Goeckerman[8] advocated the treatment of lupus erythematosus by the application of filtered roentgen rays to the regions of the body that contained lymph nodes in a manner similar to that employed in treatment of Hodgkin s disease and other types of lymphoblastoma Marked improvement and temporary involution of the lesions occurred in about half of the cases of chronic disseminate and subacute disseminate lupus erythematosus in which this treatment was employed but in many cases there were recurrences and repeated courses of treatment were necessary In two cases in each group the patients have remained free from symptoms of the disease for five to seven years after treatment was stopped Temporary improvement was obtained in three cases of the acute disseminate type In several cases roentgen therapy resulted in further dissemination of the disease and in two instances typical lesions of lupus erythematosus which were limited to regions of skin exposed to the rays developed Systemic roentgen therapy is contraindicated in the presence of marked anemia or leukopenia and hence in most cases in which the disease is of the acute disseminate type

Best results in the treatment of chronic or subacute types of lupus erythematosus at the Mayo Clinic occurred in those cases in which patients received one or more courses of systemic roentgen therapy followed by one or more courses of gold sodium thiosulfate Five patients who had the chronic disseminate type of the disease and three who had the subacute disseminate type have remained free from symptoms of the disease for as long as ten years since treatment was stopped Several others have been kept in a reasonably good state of health for several years by the combined use of the two methods of treatment

No apparent cure resulted from the use of gold alone and no one of the patients in the cases of acute disseminate lupus in which gold therapy was employed was able to complete a full course of treatment Several patients with chronic and subacute disseminate lupus erythematosus

have been able to control recurrent attacks by taking one or two courses of gold sodium thiosulfate a year for a period of several years Recurrences however almost invariably are the rule as emphasized by Calloway and Stokes[10] who said that these recurrences usually occur in the summer after the patient has been exposed to the sun

Severe toxic reactions and temporary acute dissemination occurred following the use of gold in several of the 154 cases The reactions to gold parallel those to arsphenamine and include varying degrees of dermatitis including exfoliative dermatitis ulcerative lesions in the mucous membranes toxic changes in liver and kidney and severe changes in the blood including agranulocytosis and even aplastic anemia[16, 51] A decrease in the leukocyte count a marked leukopenia and a decrease in the erythrocyte count seem to be contraindications to the continuation of gold therapy[20, 64]

The judicious use of gold therapy would seem to be of definite value in the chronic and subacute disseminate types of lupus erythematosus It is contraindicated in the acute type although Wise and Sulzberger[84] reported good results by starting with very small doses

Because of the toxic reaction to the various gold compounds injections of different types of bismuth have been employed especially by the French and English[53, 64] investigators Toxic reactions are less frequent than when compounds of gold are employed but beneficial results are not obtained as frequently or are they as striking as with the use of gold In two of our 154 cases apparent arrest of the lupus erythematosus has been obtained Beneficial results have been reported following the use of esters of chaulmoogra oil[3, 4] I believe that the use of preparations of arsenic is contraindicated Various preparations of sulfanilamide have been employed recently and the cure of a patient who had acute disseminate lupus erythematosus has been reported[1] In most cases of various types of the disease the results of treatment with sulfanilamide have not been striking Injections of tuberculin have resulted in dissemination of a localized discoid type and even in death but good results have been obtained by the careful use of tuberculin therapy[1, 6] Oro claimed that he obtained cures in 41 per cent of cases of disseminate lupus erythematosus The majority of dermatologists believe that tuberculin therapy is contraindicated Vaccine therapy of different types foreign protein mild fever therapy and the use of *ionization have had* their advocates Deficiency in vitamins especially ascorbic acid has been said to be an etiologic factor and a diet high in vitamins may be beneficial from the point of view of increasing the patient s general resistance

Evaluation of different types of treatment in the more acute dissemi

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may resemble it and also from various types of transient erythema associated with constitutional symptoms which may simulate those encountered in cases of disseminate lupus erythematosus

BIBLIOGRAPHY

1 ANDERSON H F Fulminating acute lupus erythematosus cured by sulfanilamide Arch Dermat and Syph 1938 XXXVIII 6..

2 BAEHR GEORGE, KLEMPERER PAUL and SCHIFRIN ARTHUR A diffuse disease of the peripheral circulation (usually associated with lupus erythematosus and endocarditis) Trans Assoc Am Physicians 1935 L 139

3 BARBER H W A case of acute lupus erythematosus Brit Jour Dermat 1915 XXVII 3/5

4 BARBER H W A case of lupus erythematosus associated with streptococcic infection of the tonsil Brit Jour Dermat 1919 XXXI 186

5 BELOTE G H and RATNER H S V The so-called Libman Sacks syndrome its relation to dermatology Arch Dermat and Syph 1936 XXXIII 64

6 BRUNSTING L A BRUGSCH J T and O LEARY P A Quantitative investigation of porphyrin metabolism in diseases of the skin Arch Dermat and Syph 1939 XXXIX 294

7 BYWATERS F G Personal communication to the author

8 CABOT case 4 of MALLORY T B Lupus erythematosus New England Jour Med 1938 CCXVIII 838

9 CALLAWAY J L Use of ethyl esters of chaulmoogra oil in treatment of lupus erythematosus Arch Dermat and Syph 193? XXXV 1135

10 CALLAWAY J L and STOKES J H Relapse in lupus erythematosus after treatment with sodium gold thiosulfate Arch Dermat and Syph 1935 XXXVII 6 ?

11 CANNON A B and ORNSTEIN G G The tubercle bacillus as an etiologic factor in lupus erythematosus Arch Dermat and Syph 19 , XII 691

12 CANNON A B and ORNSTEIN G G Lupus erythematosus treatment with tuberculin Arch Dermat and Syph 19 XXI ?

13 CIVATTE A Les recherches sur l etiologie du lupus erythemateux depuis ? ans Ann de Dermat et Syph 1? ? VII 465

14 CUMMER C L Lupus erythematosus in infancy and in childhood Arch Dermat and Syph 1931 XXIV 903

15 CUMMER C L Etiology of lupus erythematosus occurrence in the negro Arch Dermat and Syph 1936 XXXIII 434

16 DAMESHEK WILLIAM Aplastic anemia following the treatment of lupus erythematosus with gold sodium thiosulfate with review of the literature of hematological reactions following gold therapy New England Jour Med 1934 CCX 684

17 DAVIDSON A M and BIRT A R Quinine bisulfate as a desensitizing agent in treatment of lupus erythematosus Arch Dermat and Syph 1938 XXXVII 4

nate forms of lupus erythematosus is difficult because involution and improvement in cutaneous and systemic manifestations may occur following rest in bed On the other hand the disease may recur several years after an apparent cure

Summary

Lupus erythematosus may be regarded as a disease of unknown cause In the acute and subacute disseminate forms severe systemic toxic manifestations predominate and affect any organ in the body without causing changes in these organs that can be regarded as pathognomonic of the disease Women are affected much more frequently than are men Some of the more frequent systemic manifestations are arthralgia and arthritis anemia leukopenia and even thrombocytopenia blood dyscrasia evidence of renal irritation at times nephrosis and nephritis bacterial and nonbacterial endocarditis toxic hepatitis and splenitis effusion in serous and synovial membranes local or general adenopathy gastro intestinal symptoms and last but not least a septic type of fever In the disseminate forms of lupus erythematosus the more acute the disease the more marked are the constitutional symptoms and the more serious becomes the prognosis In many cases a streptococcic infection plays a major role Infrequently an active tuberculosis is found The reticulo-endothelial system of the entire body may be involved but there is no evidence that lupus erythematosus is a primary disease of this system Fatal termination is the rule in the acute disseminate forms usually as a pneumonia which is associated at times with pleurisy pericarditis and endocarditis

Treatment of the more acute disseminate forms consists of rest in bed local and general supportive measures including blood transfusion strict avoidance of exposure to light oral administration of quinine and if the disease should become quiescent the judicious use of systemic roentgen therapy to the lymph nodes together with the most cautious use of compounds of gold and bismuth and the most cautious and gradual removal of foci of infection

Diagnosis of lupus erythematosus is dependent on recognition of the lesions in the skin Cutaneous histopathological studies often are of value in establishing the correct diagnosis All types of transitions between a localized benign chronic discoid lupus erythematosus and the acute disseminate forms of lupus erythematosus occur These types cannot be regarded as separate diseases It is important to distinguish disseminate lupus erythematosus from other types of dermatitis that

38 KEIL HARRY Relationship between lupus erythematosus and tuberculosis a critical review based on observations at necropsy Arch Dermat and Syph 1933 XXVIII 765

39 KEIL HARRY The so called Libman Sacks syndrome Arch Dermat and Syph 1936 XXXIV 1 4

40 KEIL HARRY Relation between systemic lupus erythematosus and a peculiar form of thrombocytopenic purpura Brit Jour Dermat 1937 XLIX 1

41 KEIL HARRY Conception of lupus erythematosus and its morphologic variants with particular reference to systemic lupus erythematosus Arch Dermat and Syph 1937 XXXVI 7 9

42 KEIL HARRY Tuberculous skin lesions New England Jour Med 1938 CCXVIII 783

43 KEIL HARRY The rheumatic erythemas a critical survey Ann Int Med 1938 XI 3

44 KEITH N M and ROWNTREE L G A study of the renal complications of disseminated lupus erythematosus report of four cases Tran Assoc Am Physicians 19 XXXVII 487

45 KELLER R J ARNOTT W M and MATTHEW G D Observations on the morbid histology of the kidneys in eclampsia and other toxemias of pregnancy Jour Obst and Gynec Brit Emp 193 XLIV 3 0

46 KREN OTTO Zur Klarung der Pathogenese des Lupus erythematodes acutus Wien med Wchnschr 1936 LXXXVI 680

47 LEGOBBE I Familiarer Erythematodes Zwei Todesfalle bei einer Beobachtung tuberkuloser Organbefund Dermat Wchnschr 193 CV 1145

48 LIBMAN EMANUEL and SACKS BENJAMIN A hitherto undescribed form of valvular and mural endocarditis Arch Int Med 1924 XXXIII 701

49 LOMHOLT SVEND Antileprolbehandlung bei Lupus erythematodes Dermat Wchnschr 1935 CI 81

50 LOW C R and RUTHERFORD ANDREW Post mortem report on a case of lupus erythematosus Brit Jour Dermat 1930 XXXII 3 6

51 LUDY J B and CORSON E F Lupus erythematosus increased incidence hematoporphyrinuria and pectroscopic finding Arch Dermat and Syph 1938 XXXVII 403

52 LYON J M Acute lupus erythematosus Am Jour Dis Child 1933 XLV

53 MACKENZIE K M B Treatment of lupus erythematosus with bismuth Lancet 1930 I 1 8

54 MADDEN J F Acute disseminated lupus erythematosus Arch Dermat and Syph 193 XXX 854

55 MARTENSTEIN HANS and CRANZOW-IRRGANG DOROTHEA Über positive Luetin Reaktionen bei Lupus erythematodes (Mit Bemerkungen über die Beziehung von Luetin und Jodkali) Arch f Dermat u Syph 1926 CLII 1 6

18 DENZER B S and BLUMENTHAL SIDNEY Acute lupus erythematosus disseminatus Am Jour Dis Child 1937 LIII 525

19 DIASIO F A Lupus erythematosus a pathological survey, Med Jour and Rec 193 CXXXVI 72

20 EHRMANN S and FALKENSTEIN FRITZ Über Lupus erythematodes Arch f Dermat u Syph 1922 CXLI 408

21 ENGMAN M F JR Early acute lupus erythematosus Arch Dermat and Syph 1937 XXXV 685

22 FRESHWATER DOUGLAS The aetiology of lupus erythematosus Brit Jour Dermat 191 XXIV 57

23 GALLOWAY JAMES and MACLEOD J M H Erythema multiforme and lupus erythematosus their relationship to general toxemia Brit Jour Dermat 1903 XV 81

24 GAWALOWSKI KAREL Lupus erythematodes acutus Acta Dermat Venereol 1929 X 1

25 GENNERICH WILHELM Über die Ätiologie des Lupus erythematodes Arch f Dermat u Syph 1921 CXXXV 184

26 GOECKERMAN W H Is lupus erythematosus discoides chronicus due to tuberculosis? Arch Dermat and Syph 1921 III 788

27 GOECKERMAN W H Lupus erythematosus as a systemic disease Jour Am Med Assoc 1923 LXXX 54

28 GOECKERMAN W H The treatment of lupus erythematosus by filtered x rays to the glandbearing region of the body Med Jour and Rec 1924 CXX 530

29 GOECKERMAN W H and MONTGOMERY HAMILTON Lupus erythematosus an evaluation of histopathologic examination Arch Dermat and Syph 1932 XXV 304

30 HECHT J J and PERRIN S R The value of blood studies in the treatment of lupus erythematosus Pennsylvania Med Jour 1938 XLI 1006

31 HINCKLEY R C and McKINLAY C A Acute disseminated lupus erythematosus associated with miliary tuberculosis Minnesota Med 1938 XXI 422

32 JADASSOHN J Lupus erythematodes In Mracek Handbuch der Hautkrankheiten III pp 298–424 Wien Alfred Holder 1904

33 JADASSOHN J Dermatologie pp 630–637 Weidmann and Co Wien 1938

34 JARCHO SAUL Lupus erythematosus associated with visceral vascular lesions a series of autopsied case Bull Johns Hopkins Hosp 1936 LIX 262

35 JELINSKY B W Über die Cholesterinämie bei Lupus erythematodes Dermat Wchnschr 1933 XCVI 739

36 KAPOSI Neue Beiträge zur Kenntnis des Lupus erythematosus Arch f Dermat u Syph 1872 IV 36

37 KEEFER C S and FELTY A R Acute disseminated lupus erythematosus report of three fatal cases Bull Johns Hopkins Hosp 1924 XXXV 294

75 STICKNEY J M The lesions of the kidney in disseminated lupus erythematosus (thesis) Unpublished data

76 STÜMPKE GUSTAV Zur Atiologie des Lupus erythematodes Dermat Wchnschr 1926 LXXXII 83

77 TAUSSIG LAURENCE The Senear Usher syndrome variety of lupus erythematosus Arch Dermat and Syph 1933 XXVII 498

78 VEIEL FRITZ Lupus erythematodes (Cazenave) In Jadassohn J Handbuch der Haut und Geschlectskrankheiten X pt I pp 687–795 Julius Springer Berlin 1931

79 VOLK R Periarteritis nodosa bei einem Lupus erythematodes chron cum exacerbatione Dermat Ztschr 1928 LIII 682

80 WAIL S S Zur Frage der Pathogenese und pathologischen Anatomie des Lupus erythematodes acutus Arch f Dermat u Syph 1930 CLXI 43

81 WEIDMAN F D and GILMAN R L A case of acute disseminated lupus erythematosus necropsy disclosing acute endocarditis but not tuberculosis Brit Jour Dermat 1931 XLIII 641

82 WELSH A L Specificity of streptococcus isolated from patients with pemphigus preliminary report Arch Dermat and Syph 1934 XXX 611

83 WENDT H Interne Krankheitsbilder beim Lupus erythematodes acutus Munchen med Wchnschr 1934 LXXXI 217

84 WILE U J and ARNOLD H L The Senear Usher syndrome read before ninetieth annual session of the American Medical Association St Louis Missouri May 15–19 1939

85 WISE FRED and SULZBERGER M B Year Book of Dermatology and Syphilology p 48 1938

Sept 1 1939

56 MATRAS AUGUST Zur Symptomatologie und Klinik todlich verlaufender Fälle von Lupus erythematosus Arch f Dermat u Syph 1938 CLXXVII 2 3

57 MILBRADT WILHELM Lupus erythematodes acutus und thrombopenische Purpura zugleich Bemerkungen über das Blutbild beim Lupus erythematodes Dermat Wchnschr 1937 CV 997

58 MOOK W H WEISS R S and BROMBERG L K Lupus erythematosus disseminatus Arch Dermat and Syph 1931 XXIV 786

59 OBERMAYER M E and BECKER S W Ammonium succinimido aurate a gold compound of low toxicity Jour Invest Dermat 1938 I 85

60 O'LEARY P A Disseminated lupus erythematosus Minnesota Med 1934 XVII 637

61 ORMSBY O S A Practical Treatise on Disease of the Skin for the Use of Students and Practitioners ed 5 pp 827–845 Lea & Febiger Philadelphia 1937

62 ORO AUGUSTO La tubercolinoterapie nel lupus eritematoso La Reforma Medica 1938 XLIV 275

63 OSLER WILLIAM On the visceral manifestations of the erythema group of skin diseases Am Jour Med Sc 1904 CXXVII 1

64 PAUTRIER L M Lupus Érythémateux In Darier J Sabouraud Gougerot Milian Pautrier Ravaut Sezary Clement Simon Nouvelle Pratique Dermatologique III pp 733–824 Masson et Cie Paris 1936

65 POEHLMANN A Lupus erythematodes WR und Syphilis (Bemerkungen zu der Arbeit von Donges) Dermat Wchnschr 1935 CI 1351

66 PUENTA J J Topografia del lupus eritematoso consideraciones sobre su patogenia Rev Argent de Dermat 1936 XX 613

67 ROBERTSON W F and KLAUDER J V Lupus erythematosus acutus disseminatus report of a fatal case associated with disseminated telangiectasis Arch Dermat and Syph 1923 VIII 487

68 ROGIN JAMES and O'LEARY P A Unpublished data

69 ROSE EDWARD and PILLSBURY D M Acute disseminated lupus erythematosus a systemic disease Ann Int Med 1939 XII 951

70 ROXBURGH A C Acute disseminated lupus erythematosus five fatal cases Brit Jour Dermat 1933 XLV 95

71 SCHAEFER L W The role of the streptococcus in the etiology of pemphigus lupus erythematosus and erythema group of hematogenous dermatoses Jour Michigan Med Soc 1937 XXXVI 292

72 SCHAUMANN JORGEN Sur la Pathogenie du lupus Érythémateux Ann de Dermat et Syph 1936 VII 193

73 SENEAR F E and USHER BARNEY An unusual type of pemphigus combining features of lupus erythematosus Arch Dermat and Syph 1926 XIII 761

74 SNAPPER ISIDORE Kidney trouble in acute lupus erythematosus In Berglund Medes Huber Longcope Richards The Kidney in Health and Disease p 433 Lea & Febiger Philadelphia 1935

CHAPTER LXVI

LUPUS ERYTHEMATOSUS DISSEMINATUS FROM THE POINT OF VIEW OF INTERNAL MEDICINE

By GEORGE BAEHR and SAUL JARCHO

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Definition.—Lupus erythematosus disseminatus is a constitutional disease of unknown origin which produces widespread degenerative alteration of small blood vessels and connective tissue. The morbid

Cazenave's designation lupus erythematosus Hebra's atlas depicts two forms of the disease Kaposi in 187_ suggested that these two forms be named respectively lupus erythematosus discoides and lupus erythematosus discretus et aggregatus

Kaposi[7] contributed far more than a mere improvement in nomenclature It was he who first made known the fact that certain cases of lupus erythematosus were accompanied by severe constitutional disturbances which might end in death Such cases were considered to represent the more acute instances of lupus erythematosus discretus et aggregatus Kaposi observed that lupus vulgaris was much more common than lupus erythematosus no doubt this still is true in Europe it is less and less likely to be true in America as the incidence of tuberculosis steadily decreases Kaposi also recognized that lupus erythematosus occurred more often in women than in men

It was suggested repeatedly by Boeck and others that lupus erythematosus was caused by tuberculosis This idea almost certainly owed its vitality to the high incidence of tuberculosis which prevailed at the time The use of the designation lupus for both lupus vulgaris and lupus erythematosus did nothing to diminish the confusion It is probable that the concept of lupus erythematosus disseminatus was even stretched to include cases of papulonecrotic tuberculid

The monumental treatise of Jadassohn[8] (1904) did much to clear away difficulties and restore order Jadassohn insisted that the cause of lupus erythematosus still was unknown He distinguished simply a chronic and an acute form and considered that the two might be unrelated He listed several of the important constitutional symptoms of acute lupus erythematosus and ascribed them to inundation of the organism with infectious or toxic material

In more recent years the systemic aspects of lupus erythematosus have received increasing consideration Autopsy reports continue to accumulate in small numbers In 19 4 an important advance was achieved by Libman and Sacks[9] who described four cases of an atypical form of endocarditis in two of the four cases which were described cutaneous lesions resembling those of lupus erythematosus were present In 1935 Baehr Klemperer and Schifrin[10] found lupus erythematosus in association not only with endocardial lesions but more characteristically with certain well defined alterations in the blood vessels especially those of the kidney The significance of systemic vascular alterations in association with acute lupus erythematosus was demonstrated subsequently also by Jarcho by Ginzler and Fox[11] and by Denzer and Blumenthal[12]

process strikes mainly the serous and synovial membranes kidneys and heart Involvement of the skin is usual but does not occur in every case The basic principle of the disease seems to lie in an alteration of collagen concerning the fundamental mechanisms of cause and pathogenesis almost nothing is known

History

Lupus erythematosus disseminatus like other diseases of unknown cause was originally an abstraction produced by selecting a group of patients according to special criteria Therefore, the history of the disease is largely a history of changing concepts

In the second edition of their treatise on dermatology (1833) Cazenave and Schedel[1] intercalated into their chapter on erythema the statement that Biett had described a special subgroup to which he had given the name of centrifugal erythema *(erythème centrifuge)* It has been impossible to find Biett's description if indeed he ever published one Centrifugal erythema is mentioned again in the third (1838) and fourth (1847) editions of the textbook by Cazenave and Schedel At a dermatological clinic held in Paris in 1851 Cazenave presented several additional cases of centrifugal erythema and suggested that the disease be named lupus erythematosus both designations occur in the title of Cazenave's presentation To this day lupus erythematosus is called by some Cazenave's lupus to distinguish it from lupus vulgaris (Willan's lupus) In his publications Cazenave repeatedly stated that the condition which he was describing produced no discernible impairment of the patient's general health Later authors such as Pernet[3] (1908) have felt for this reason that Cazenave's cases were chronic types and dealt with the conditions which later came to be known as fixed or discoid lupus erythematosus and symmetrical centrifugal lupus erythematosus Even the illustrious Jadassohn[4] observed that it is extremely difficult to identify these early cases the great man's comment will meet the hearty approbation of anyone who conscientiously reads the original descriptions

In 1845 Hebra undertook to classify the entire corpus of cutaneous diseases according to principles of pathology His ambitious system includes a condition designated as seborrhea congestiva which traditionally is assumed with perhaps some justification to be lupus erythematosus In 1856 Hebra[6] issued the first part of his magnificent dermatological atlas in which the term seborrhoea congestiva is replaced by

fibrin is formed but merely that fibers in their altered condition acquire a resemblance to threads of fibrin The ground substance of the pericardium often appears to be increased in amount and in hematoxylin eosin preparations may be difficult to distinguish from the fibers Similar appearances are found commonly in the pleura and occasionally in the peritoneum and the synovial membranes The serous membranes of the abdomen also may show adhesions but rarely to an important extent Perisplenitis and perihepatitis are common and also have their origin in characteristic fibrinoid changes in the connective tissues beneath the covering endothelium as in the pleura pericardium and endocardium

Heart

In the heart the most impressive changes are found in the endocardium The endocardium of the valve cusps and walls of the chambers of the heart presents gross evidences of a peculiar coarse endocarditis in 40 per cent of the cases an additional 20 per cent show smaller masses on the endocardium only on microscopic examination Grossly visible lesions take the form of granular pink verrucae usually about 3 mm in size disposed singly or in clusters on the valve leaflets cusps and chordae Mural lesions may appear as verrucae or as plaques

The lesions when studied microscopically seem to begin as minute homogeneous aggregations of eosinophilic ground substance situated beneath intact endothelium nearby the so-called myocytes proliferate In older lesions the endothelium exhibits pyknosis and becomes elevated over the subjacent pinkish masses of altered ground substance It is important to understand that a verruca is not something which has been deposited by the blood stream On the contrary it is a development which originates in the tissues of the valve and raises up the endothelial surface In late stages the verrucae are invaded by fibroblasts and blood vessels The newly formed collagenous tissue may suffer the same fibrinoid change which originally affected the valve

The verrucae occasionally are subject to bacterial implantation Where this has happened adjacent verrucae often are uninvolved and the observer is enabled to conclude that bacterial infection has been superimposed pre agonally upon a morbid process previously extant

In the myocardium foci of the connective tissue which surrounds small blood vessels and separates muscle bundles suffer the same eosinophilic transformation which occurs elsewhere in the body The

Although the elaborate study by Keil[13] destroyed or should have destroyed the hypothesis that lupus erythematosus is of tuberculous origin, the ghost of this dead idea still haunts the literature Thus the 1947 edition of a well-known French textbook[14] describes the disease under the tuberculids

The pioneers of modern dermatology classed lupus erythematosus with erythema or with seborrhea In part through an accident of nomenclature the disease later was placed in the same category with the tuberculous affections of the skin Later in the 19th century, an era of great dermatological clinicians a distinctive acute form of lupus erythematosus was recognized and was found to be accompanied by important constitutional disturbances The present tendency is to see in the scattered cutaneous and visceral lesions a common element of injured collagen A similar principle is perhaps at work in scleroderma and in rheumatic fever (Baehr and Pollack[1]) There is reason to doubt whether the morphological similarities of these diseases are pathogenetically significant This is a problem which the new era of x-ray diffraction and electron microscopy must now attempt to resolve

Pathology

Serous and Synovial Membranes

The pericardium or pleura or both are affected almost always at some stage of the disease In the majority of instances there is diffuse or focal pericarditis which leads to extensive adherence of the visceral and parietal layers The process may obliterate the pericardial sac and may extend to implicate the pleura The epicardial tissues often appear grossly thickened and gelatinous

Even when the pericardium appears normal to the naked eye, microscopic examination often discloses fibrosis and vascularization of the epicardial adipose tissue and the presence of large fibroblasts Especially characteristic is the presence of a deeply eosinophilic substance around and between the collagen fibers in the stratum proprium of the epicardium This conspicuous eosinophilic substance is believed to arise by physicochemical alteration of the interfibrillar ground substance At the same time the collagen fibers of the epicardium become straight thick and also intensely eosinophilic This change in the fibers has been designated fibrinoid degeneration the term is not intended to suggest that

In extreme cases the "wire loops" become fragmented, focal necrosis may occur. In some instances focal necrosis of segments of glomeruli is observed in the absence of the "wire loop" lesion. The tubules of the renal cortex show no significant abnormality unless glomerulonephritis or arteriolar necrosis is present concomitantly, in consequence of fibrinoid degeneration in the walls of small renal vessels. Where occlusion of a diseased artery or arteriole has occurred, the affected segment of renal parenchyma may undergo necrosis or atrophy. In a few instances this has been sufficiently conspicuous throughout the renal cortex to produce gross pitting of the surface of the kidney and an appearance resembling that of malignant nephrosclerosis.

Blood Vessels

In the various viscera and tissues of the body the walls of small arteries and precapillary arterioles frequently are involved by the disease process. The condition of the blood vessels in lupus erythematosus disseminatus is important not only because these structures are ubiquitous and indispensable but also because the morphological character of their involvement affords insight into the nature of the disease. The minimal lesion consists of a deposit of uniformly eosinophilic "fibrinoid" matter within the intima or among the muscle fibers of the media or within the adventitia. In ordinary hematoxylin-eosin preparations the pinkish deposit appears to be structureless. Fibroblastic proliferation often is to be found nearby. At this stage the superjacent intima looks normal even although the lumen of the vessel may be narrowed. In more advanced lesions the intima may contain complete rings of eosinophilic material; these traverse the internal elastic lamella to fuse with similar accretions in the media and adventitia. In a small minority of cases the fibrinoid alteration of vascular collagen is associated with widespread necrosis of muscular and elastic lamellae; the concomitant inflammatory exudate is chiefly mononuclear. The necrotic tissue sometimes is invaded by fibroblasts. Although occlusion of the lumina of affected arteries by cellular detritus is common, thrombosis and hemorrhage are infrequent. Veins are not often involved.

Skin

In the skin the ground substance of the corium gives rise to small clumps of homogeneous eosinophilic material; at the same time the colla-

accompanying cellular infiltrates may bear a superficial resemblance to the Aschoff bodies encountered in rheumatic fever. However, the eosinophilic interstitial lesions in lupus erythematosus remain predominantly degenerative with relatively few intact cells and little or no tendency to fibrosis.

Fibrinoid degeneration of connective tissue may occur also in the walls of the smaller coronary arteries. The vascular lesions in the heart may be accompanied by focal necrosis and atrophy of muscle fibers.

Spleen and Lymph Nodes

The spleen usually shows little if any enlargement; the central and penicilliary arteries often are surrounded by thick rings of collagen arranged in concentric fashion about the vessels. This onion-skin appearance is produced presumably by a characteristic transformation of argyrophilic reticulum.

The lymph nodes, which usually are enlarged so as to be palpable in all regions of the body, show a diffuse hyperplasia which may proceed in some instances to actual necrosis without any peripheral connective tissue reaction. Although this bears no resemblance to caseation, it has been mistaken for the evidences of tuberculosis.

Kidneys

While the gross appearance of the kidneys ordinarily reveals little more than a moderate increase in size and weight and perhaps a fine-grained hemorrhagic mottling, the microscopic appearances are extensively and distinctively altered. The attention of the observer is attracted at once by the glomeruli, many of which contain one or more thickened intensely eosinophilic loops. Sometimes the thickness of the capillary walls of affected glomerular loops and their intense coloring are reminiscent of the heavily accented lines in a crayon sketch. These are customarily called "wire loop" lesions. The eosinophilic deposits, which produce this appearance, lie between the endothelium of the glomerular capillaries and the visceral layer of Bowman's capsule; for this reason they stand out most conspicuously in the peripheral parts of the glomerulus, although closer inspection reveals their presence even at the center. The lesions react negatively to tests for amyloid.

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gen fibers become thick, straight and intensely eosinophilic These changes are most prominent in the superficial layers of the corium and the cutaneous papillae In more advanced lesions the fibrinoid masses and the altered collagen fibers undergo fragmentation and often become partly basophilic These changes are accompanied by proliferation of fibroblasts by dilatation of capillaries and by extravasation of blood Definite inflammatory exudates are uncommon The epidermal cells show vacuolization and when the subcutaneous tissue is profoundly altered the basal cell layer occasionally may become necrotic

In some instances the skin may show minimal alterations in its connective tissue even although extensive changes may be present in the viscera and in the deeper connective tissues of the body

Other Viscera

Foci of fibrinoid degeneration usually can be found in the loose connective tissues of the mediastinum the retroperitoneal space and of any organ or part of the body although gross abnormalities are rarely visible

In a few instances in which death has occurred after a short and fulminating course a careful gross and microscopic study of the tissues may be unrewarding Although the lungs may at times show the vascular lesions seen in other viscera a common finding is bronchopneumonia, obviously the result of a terminal infection

Incidence

The disease still is unfamiliar to many internists not so much because of its rarity as because the patients are apt to be under the care of dermatologists on account of the rash In those in whom the characteristic erythema fails to appear the disease may escape recognition because of resemblance of many of its clinical manifestations to those of rheumatic fever and rheumatoid arthritis

One of the most remarkable characteristics of the disease is its sex linkage About 95 per cent of the cases occur in young females usually in the second and third decade of life Although the disease begins in most instances between puberty and menopause we have observed it occasionally in children as young as 6 or 7 years of age The oldest

patient in our experience was 45 years old When it occurs in males usually they are boys or young adults Cases have been observed simultaneously in siblings

Etiology and Pathogenesis

A bacterial agent has never been identified The streptolysin titre of the serum is not elevated as a rule Even during the febrile periods blood cultures are consistently negative unless there is an intercurrent pneumonia a terminal blood invasion by streptococci or staphylococci or a complicating acute infection of the endocardium with one of these bacteria The serum Wassermann or other test for syphilis may be negative or it may fluctuate between various degrees of positivity or even be anticomplementary A positive reaction is non specific It has been ascribed by Coburn and Moore to the high globulin content of the serum but there is no conclusive evidence to support this conclusion Similar high serum globulin levels may be observed in other prolonged wasting diseases especially those due to chronic infections

As in rheumatic fever and rheumatoid arthritis infection probably is responsible for the disease either primarily or indirectly but its nature has not been determined The special predisposition of females would seem to indicate that whatever the exact nature of this infection or intoxication the disease is conditioned upon a peculiarity in the constitutional reaction of the host

Teilum[1, 2] recently has attempted to relate the disease to allergy but he has not demonstrated a specific allergin or adduced adequate clinical or pathological evidence in support of this hypothesis In this contention he has followed the lead of Rossle[3] and of Rich and Gregory[4] who relate rheumatic fever and periarteritis nodosa to allergy because they regard the occurrence of fibrinoid changes in the connective tissues in all these diseases as a common denominator There can be little doubt that periarteritis nodosa is an allergic disturbance affecting the vascular system of the body for it is commonly observed in sufferers from asthma or urticaria and is associated as a rule with eosinophilia of the blood or tissues Vascular lesions similar to those of periarteritis can be reproduced experimentally by the repeated intravenous injection of heterologous serum proteins or bacteria The evidence in support of an allergic pathogenesis for rheumatic fever still is precarious for it consists solely in the fact that recurrences of the disease often follow

streptococcal infections and that streptolysin may appear in high titre in the blood

The occurrence of fibrinoid degeneration of collagen in the Aschoff bodies and other foci of connective tissue reaction in rheumatic fever disseminated lupus erythematosus, diffuse scleroderma the Arthus phenomenon and in serum sickness is not acceptable as evidence that all these so called rheumatoid diseases are allergic or hyperergic Similar fibrinoid changes are often as conspicuous in the connective tissue at the base of a peptic ulcer, around a foreign body, in the walls of diseased vessels in tuberculous meningitis following injury to connective tissue by the leakage of pancreatic secretion in acute pancreatitis and in the arteries of rats in whom malignant hypertension has been produced by the Goldblatt experiment

It is therefore apparent that fibrinoid degeneration may result from varied types of injury to the connective tissue and is not specific for any one type The conspicuous absence of allergic phenomena such as asthma urticaria and eosinophilia during the clinical course of disseminated lupus erythematosus or of diffuse scleroderma and the fact that these diseases do not occur characteristically in members of atopic families speak against the hypothesis that they are due to hypersensitivity to some unknown agent

The occurrence of 95 per cent of the cases among females had led clinicians to search for an endocrine disorder but no abnormalities have been found in the glands of internal secretion nor have the male patients shown any endocrine stigmata Exacerbations of the disease are not related to the menstrual cycle Although menstruation may become irregular or even cease during the progress of the disease this is observed also in other prolonged debilitating illnesses associated with anemia

The protracted clinical course with its exacerbations and remissions may be accelerated in its later stages by intercurrent bacterial infections The clinical manifestations can be intensified also by a variety of other untoward factors such as nutritional deficiency sunburn and exposure to wind and to extremes of temperature but none of these influences is more than secondary in significance

Clinical Course

Fever — The symptoms commence in the guise of prolonged sieges of irregular fever and weakness The fever may be regarded as an index

of the activity of the disease at any given moment but it is only one index and only an approximate index When the disease is completely in abeyance or in remission fever is absent Quite commonly the fever takes onset in the form of small elevations which for a time may even escape the notice of the patient Often the patient will complain of indefinite uneasiness or mild weakness while an exact record reveals a daily rise to *100 F* each *afternoon* and a daily *fall to 98 or 98 2 F* in the early morning Exacerbations and important complications in the clinical course are almost always accompanied by frank elevations to *10 or 104 F or more* Such elevations *may be sustained for weeks or* months and are especially common when serous effusions or pulmonary inflammations are developing A swinging or so called septic temperature *often is observed even although the blood culture is sterile*

Inflammation of Synovial and Serous Membranes — From time to time the clinical course is diversified by attacks of arthralgia pleuritis pericarditis or abdominal pain *Pain in the joints is more common then* and the arthralgia tends to shift from one location to another If the cutaneous rash has not made its appearance or has escaped detection the diagnostic problem is apt to be puzzling *an incorrect diagnosis of rheumatic* fever or rheumatoid arthritis is difficult to avoid at this stage Attacks of pleuritis and pericarditis are as common as in rheumatic fever and may be associated with a *serous effusion* In some instances the serositis may involve the peritoneum so as to give rise to abdominal pain tenderness rigidity and an erroneous suspicion of intra abdominal inflammatory disease

Heart — Heart murmurs are absent or inconspicuous they often disappear when the fever remits When they are heard they are therefore *impossible to identify as evidence of endocarditis Cardiac* insufficiency is rare pericarditis common During acute febrile exacerbations of the illness gallop rhythm is encountered frequently The electrocardiogram rarely is abnormal *except for the low voltage characteristic of* any wasting disease unless pericarditis is present

Lymph Nodes and Spleen — The superficial lymph nodes usually are enlarged *but the spleen ordinarily is not palpable unless there is an* intercurrent bacterial infection of the blood stream In one series of 3 patients the authors found the spleen to be enlarged and palpable in 4

Leukopenia and Hematuria — Leukopenia and microscopic hematuria are almost always present during exacerbations and are comparatively reliable diagnostic signs The presence of an obscure fever and arthralgia in a young woman who has leukopenia and who is found to

streptococcal infections and that streptolysin may appear in high titre in the blood

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tracing prepared from the serum of a patient who suffered from disseminated lupus erythematosus In this tracing the gamma globulin is seen to be greatly increased and is represented by an area approximately three times as large as the normal In the same diagram the serum albumin fraction represented by the area under the tall sharp curve at the extreme right is decreased In this instance the alpha globulin fraction is increased to about double the normal In uncomplicated cases the blood culture is sterile and the bacterial flora of the upper respiratory is not abnormal

Cutaneous Lesions — At any period in the clinical course the cutaneous eruption may make its debut The rash may be the first manifestation of the illness in a person who previously had complained only of weakness and malaise or it may not appear until the terminal period In some instances it fails to make its appearance throughout the disease In a few patients it has appeared on the hands and feet although the characteristic areas of the face were not involved

Most often it presents itself as a number of slightly elevated erythematous plaques discrete or confluent situated on the bridge of the nose the malar eminences and cheeks As it spreads the erythematous spots tend to merge and may extend to the skin on the prominences above the eyebrows on the upper lip chin and pinna When confluent the erythema over the bridge of the nose and the cheeks presents a butterfly pattern The V shaped flush area over the manubrium often is involved

Deep seated erythematous spots are observed at times also on the fingertips and on the tips of the toes When the fingertip lesions become confluent they may spread laterally around the nail beds Without lesions on the fingertips erythematous lesions may develop at the bases of the fingernails During intense febrile exacerbations similar deep seated erythematous lesions often are present on the thenar and hypothenar eminences and on the palms and soles Areas of skin which over lie joints or are otherwise subjected to repeated mild trauma are apt to become erythematous especially over the shoulders elbows knees and malleoli

In all these sites the erythematous areas may be encountered During exacerbations of the disease the red color increases in intensity and may assume a purplish cast In the midst of the erythema petechial or purpuric specks or even hemorrhagic vesicles sometimes are present The mucosae also may show groups of small petechiae or patches of erythema which soon develop into shallow ulcers These occur chiefly on the palate and

have red cells in a catheter specimen of urine, warrants a suspicion of disseminated lupus erythematosus even in the absence of the characteristic cutaneous manifestations. Although leukopenia is one of the most constant features of the disease, the total white cell count usually is between 3,000 and 6,000, rarely dropping below 4,000. The differential leukocyte count is normal or shows a shift to the left.

If pneumonia or other infections are present intercurrently, the leukopenia may be replaced by temporary leukocytosis. Moderate thrombocytopenia and mild hypochromic anemia are usual. The tendency to depression of hematopoiesis is more marked in the later stages of the disease and the thrombocytes then may drop below 70,000. The Wassermann reaction and other serum reactions for syphilis usually are negative but at times they may be falsely positive or anticomplementary.



FIG. 1. Lupus Erythematosus—Electrophoretic diagram of serum. Note the conspicuous curve produced by gamma globulin. (Courtesy of Miss M. Reiner, Chemistry Laboratories, Mount Sinai Hospital, New York.)

Blood Globulin. — Analyses of the blood may reveal various degrees of hypoproteinemia; in advanced stages of the disease this may be severe and may be accompanied by edema of the subcutaneous tissues. In the series of 15 cases studied by Coburn and Moore[9] inversion of the albumin-globulin ratio was found in every instance although the total protein usually was within the normal range. The gamma globulin values were markedly elevated. It was found that inversion of the albumin-globulin ratio followed and did not precede the development of the symptoms of lupus, that the progress of the disease was accompanied by an increase in gamma globulin, and that return to a quiescent state was attended by a decrease in globulin. Electrophoretic analysis showed that the hyperglobulinemia characteristic of lupus was attributable chiefly to increase in the gamma fraction. Figure 1 shows an electrophoretic

Diagnosis

The presence of lupus erythematosus disseminatus should be suspected in a young woman who has had prolonged fever of unknown origin especially if attacks of arthralgia pleuritis or pericarditis have occurred The presence of microscopic hematuria weighs heavily in favor of the diagnosis and against rheumatic fever and rheumatoid arthritis Leukopenia is another helpful diagnostic sign as well as the occurrence of characteristic retinal lesions The Libman Sacks form of endocarditis which has been described as occurring in a minority of the cases does not lead to the development of valvular stenosis or insufficiency bacterial implantation may occur on such vegetations secondarily but is uncommon and usually subterminal

The cutaneous lesions of lupus erythematosus disseminatus are present in the fully developed typical case Occasionally they are inconspicuous or absent *moreover their presence is not essential to the diagnosis* The physician *should remember that discrete or confluent patches of malar erythema are in themselves no proof that lupus erythematosus disseminatus is present* That diagnosis should not be offered unless evidence of constitutional illness is found

Hargraves Richmond and Morton have recently described a new cell type which they call the L E cell This cell is a phagocyte usually a polymorphonuclear leukocyte containing a large mass of chromatin which stains deep purple with the Wright stain The cells are in heparinized samples of bone marrow and in the buffy coat of centrifugalized heparinized blood They are not present in all cases of lupus erythematosus disseminatus and their value in differential diagnosis is as yet uncertain

Treatment

For this disease so insidious in its onset and so pervasive in its effects we have as yet no efficient treatment and no preventive Antibiotic drugs are without effect in the uncomplicated case although they are useful in the control or prevention of secondary invasions with bacteria of the respiratory tract or skin Treatment is limited to general constitutional measures, individual symptoms or complications being dealt with as they arise *A vigorous effort must be made to support the patient s nutritional* condition for this is a prolonged and wasting illness For this purpose

buccal mucosa and tend to heal readily. During periods of remission the erythema in the affected areas of skin may fade completely or may leave a brown residuum. In cases of long standing, telangiectasia and areas of cutaneous atrophy may be observed.

The cutaneous lesions may appear for the first time after the skin has been exposed to sunlight. Occasionally it is ascertained that heliotherapy had been employed for the relief of arthralgia or for general tonic effect and was followed by the emergence of the ominous red blotches. Although the most exposed areas of the face and in women, of the anterior chest, are affected by sunlight, this seems to be due to the extreme sensitivity to trauma of the capillaries and subcutaneous tissues of the skin, for the same type of erythematous reaction can be induced by exposure to wind or by mechanical rubbing. The phenomenon is therefore not an example of the true photosensitivity observed in porphyrinemia or hydroa aestivale.

Vascular Lesions. — The vascular lesions often can be recognized in the eyegrounds[19] where perivascular hemorrhages and fluffy exudates appear about the arterioles and the retina may even present a circumpapillary edema. Although these retinal lesions may present a superficial resemblance to those seen in malignant hypertension, they occur in the presence of normal blood pressure and they can be distinguished also by the absence of retinal arteriosclerosis or angiospasm. In periods of relapse the urine almost always contains numbers of erythrocytes.

The *blood pressure* usually is normal throughout the illness, although a few patients ultimately may develop a moderate elevation in the systolic and diastolic pressures in the late stages, if there is extensive renal damage and beginning azotemia.

Duration. — The clinical course thus established may be protracted for months or years,[6] periods of partial or complete remission alternating with fevered relapses during which the cutaneous and mucosal lesions effloresce or extend, while the serous and synovial membranes and the vasculature suffer the changes already described. In an occasional fortunate patient the disease enters an apparently permanent remission. The majority die after a series of remissions and exacerbations, either because of renal insufficiency, intercurrent infection with streptococci, staphylococci or pneumococci or because of exhaustion. Death may occur after a few months of fulminating illness or after an irregular and protracted course extending over several years.[6] We recently observed a patient in whom the disease had lasted 11 years.

cated If there is a tendency to gallop rhythm or other evidence of impending heart failure intravenous fluids should be avoided or small transfusions of not more than 250 c c at a time should be administered at a rate not in excess of 60 drops a minute

BIBLIOGRAPHY

1 CAZENAVE A and SCHEDEL H E Abrege Pratique des Maladies de la Peau Seconde Edition Paris 1833

CAZENAVE A Lupus erythemateux (erytheme centrifuge) Ann des Mal de la Peau et de la Syph 1851 III 97

3 PERNET G Le Lupus Erythemateux Aigu d Emblee These de Paris 1908

4 JADASSOHN J Lupus Erythematodes vol 3 pp 298 4 4 in Mracek F Handbuch de Hautkrankheiten Alfred Holder Vienna 1904

5 HARGRAVES M M RICHMOND H and MORTON R Presentation of two bone marrow elements the tart cell and the L E cell Proceed Staff Meet Mayo Clinic 1948 XXIII 5

6 HENCH P S KENDALL E C SLOCUMB C H and POLLEY H F The effect of a hormone of adrenal cortex (17 hydroxy 11 dehydrocorticosterone compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis preliminary report Proceed Staff Meet Mayo Clinic 1949 XXIV 181

7 HEBRA F Versuch einer auf pathologische Anatomie gegrundeten Eintheilung der Hautkrankheiten Zeitschr d k k Gesellsch d Aerzte zu Wien Zweiter Jahrgang 1845 I 34 143 and 11

8 HEBRA F and ELFINGER A Atlas der Hautkrankheiten Text von Ferdinand Hebra Bilder von Anton Elfinger Herausgegeben durch die Kaiserliche Akademie der Wissenschaften Braumuller Wien 1856 1876

9 KAPOSI M Neue Beitrage zur Kenntniss der Lupus erythematosus Arch f Dermat u Syph 187 IV 36

10 LIBMAN E and SACKS B A hitherto undescribed form of valvular and mural endocarditis Arch Int Med 19 4 XXXIII 701

11 BAEHR G KLEMPERER P and SCHIFRIN A A diffuse disease of the peripheral circulation usually associated with lupus erythematosus and endocarditis Trans Assoc Am Physicians 1935 L 139

12 JARCHO S Lupus erythematosus associated with visceral vascular lesions a series of autopsied cases Bull Johns Hopkins Hosp 1936 LIX 6

the ordinary foods are adequate especially if supplemented with both fat soluble and water soluble vitamins When vitamin or other nutritional deficiencies are observed they are usually an indirect result of the disease which is often associated with pronounced anorexia

Recent reports by Hench Kendall, Slocumb and Polley suggest that the disease process may be alleviated at least temporarily by the use of adrenocorticotropic pituitary hormone (ACTH) or by cortisone At the moment of writing these substances represent the greatest therapeutic promise which contemporary investigation has been able to offer

The patient should at all times be kept away from the sunlight, even when the malady is in remission During acute exacerbations the window shades should be drawn or the window panes covered with red cellophane The cutaneous lesions ordinarily require nothing more than a bland ointment

Because the disease occurs almost exclusively in women bilateral oophorectomy has been employed as well as the artificial induction of the menopause by x ray therapy to the ovaries It is doubtful whether the few temporary remissions which have been observed can be ascribed to these procedures The administration of testosterone propionate in doses sufficient to induce masculinization has been tried many times but with doubtful success The dose should begin with 50 milligrams given every other day intramuscularly

Remission occurs so frequently without obvious cause that many forms of therapy have come to be relied on such as colloidal gold and even bismuth In our experience these substances are not only therapeutically worthless but their use is more dangerous in this disease than in rheumatoid arthritis for here bone marrow function is already depressed and renal damage may be advanced A toxic agent such as colloidal gold which may exert its deleterious action on the bone marrow to a degree sufficient to induce thrombocytopenia or granulocytopenia and on the renal parenchyma is therefore distinctly contraindicated

The most recent therapeutic agent to be tried is rutin Because of its reputed effect upon capillary fragility recently it was subjected by us to therapeutic trial in this disease but without demonstrable benefit

Pyrexia and arthralgia usually may be alleviated with salicylates as in rheumatic fever, and the drug also may have a favorable influence upon the resorption of serous effusions It is especially effective if employed in large doses as recommended by Coburn for rheumatic fever When edema due to hypoproteinemia and anemia are observed in advanced stages of the disease transfusions with whole blood or plasma are indi

CHAPTER I-CII

PERIARTERITIS NODOSA

By GEORGE BAEHR AND SAUL JARCHO

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Definition —Periarteritis nodosa is an uncommon obscure inflammatory disease of small and middle sized arteries The walls of affected vessels tend to become infiltrated and surrounded by localized masses of exudate If the media is damaged a vessel may undergo local aneurysmal dilatation so that a small periarteritic nodule is produced To these nodules the disease owes its name although grossly discernible nodules are *not observed in the majority of cases The absence of periarteritic nodules* has persuaded some clinicians and pathologists to rename the disease polyarteritis

Because the disease process affects specifically connective tissue of blood vessels and other vascular structure of mesenchymal origin periarteritis nodosa has been included in the general category of the collagen diseases

History

In 1866 the distinguished clinician Adolf Kussmaul and his colleague Rudolf Maier[1] reported the puzzling case of a 27 year old man who

13 GINZLER J M and FOX T T Disseminated lupus erythematosus Arch Int Med 1940 LXV 6
14 DENZER B S and BLUMENTHAL S Acute lupus erythematosus disseminatus Am Jour Dis Child 1937 LIII 5-3
15 KEIL H Relationship between lupus erythematosus and tuberculosis a critical review based on observations at necropsy Arch Dermat and Syph 1933 XXVIII 765
16 DARIER J CIVATTE A and TZANCK A Precis de Dermatologie Cinquieme Edition par A Civatte Masson Paris 1947
17 BAEHR G and POLLACK A Diffuse vascular diseases Modern Concepts of Cardiovascular Dis 1946 XV No 12
18 KLEMPERER P POLLACK A D and BAEHR G Pathology of disseminated lupus erythematosus Arch Path 1941, XXXII 569
19 FOX R A and ROSAHN P D Lymph nodes in disseminated lupus erythematosus Am Jour Path 1943 XIX 73
0 KAISER I H Specificity of periarterial fibrosis of spleen in disseminated lupus erythematosus Bull Johns Hopkins Hosp 194 LXXI ,1
1 WAGENER H P Retinal lesions in acute disseminate lupus erythematosus Am Jour Med Sci 1946 CCXI -40
2 COBURN A F and MOORE D H Plasma proteins in disseminated lupus erythematosus Bull Johns Hopkins Hosp 1943 LXXIII 196
23 TEILUM G Miliary epithelioid cell granulomas in lupus erythematosus disseminatus Acta Pathol et Microbiol Scandinav 1945 XXII 73
-4 TEILUM G Pathogenetic studies on lupus erythematosus disseminatus and related diseases Acta Med Scandinav 1946 CXXII 1 6
5 ROSSLE R Zum Formenkreis der rheumatischen Gewebs veranderungen Virch Arch f path Anat u Physiol 1933 CCLXXXVIII 780
-6 RICH A R and GREGORY J E Experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity Bull Johns Hopkins Hosp 1943 LXXII 65
27 SOMPAYRAC L and HAILEY H E Lupus erythematosus with false positive Kahn reactions Arch Dermat and Syph 1944 XLIX 355
8 HORSTMANN D M Acute disseminated lupus erythematosus with 7 year recovery case report Jour Pediat 1945 XXVII 35

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Because the disease process affects specifically connective tissue of blood vessels and other vascular structure of mesenchymal origin, periarteritis nodosa has been included in the general category of the collagen diseases.

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In 1866 the distinguished clinician Adolf Kussmaul and his colleague Rudolf Maier[1] reported the puzzling case of a 27 year old man who

suffered from fever and myalgia The patient was found to have 'chlorotic marasmus' and weakness and atrophy of muscle groups Small nodules were palpable in the subcutaneous tissues The problem was further complicated by the presence of albuminuria and hematuria Post mortem examination revealed a nodular thickening of numerous arteries of the caliber of the hepatic artery or smaller Diseased vessels were found in the stomach, intestines kidneys spleen heart and voluntary muscles Milder involvement was observed in the liver and subcutaneous tissues For this unusual disease of blood vessels Kussmaul and Maier proposed the name periarteritis nodosa It is now recognized that an earlier though less satisfying description must be credited to the observant Carl von Rokitansky and Boyd[3] by a meticulous survey of the older literature has brought to light reports which go back as far as 1766 These precede but in no sense supersede the contribution of Kussmaul and Maier whose work may be said to have launched periarteritis nodosa as an entity

Additional case reports accumulated slowly during the last decades of the nineteenth century For a time it seemed that the disease was limited to Germany and Austria actually this was an illusion and was due to the superior facilities which those countries possessed for the study of pathological anatomy As more and more cases were recorded inevitably there were reports of occasional instances in which the diagnosis had been made intra vitam on surgically excised gallbladders or appendices or even on subcutaneous nodules excised for biopsy In the present era, correct antemortem diagnosis is achieved with increasing frequency

Speculation as to the cause of the disease ran a wide gamut Kussmaul and Maier suspected trichiniasis For some years syphilis was held to be the villain, this hypothesis was dispelled by advances in pathological anatomy which defined the characteristics of syphilitic diseases of vessels Various bacteria were temporarily incriminated and transmission was attempted in experimental animals[4] Even filterable viruses were not ignored in the search for a cause The failure of such investigations lent strength to the possibility that periarteritis nodosa might be a nonspecific result[5, 6] of the damage produced by organisms of varied types Manges and Baehr[7] showed that the clinical course might even be protracted until healing had obliterated all traces of periarterial inflammation

A new approach resulted from the researches of Pirquet[8] Arthus[9], and Richet[10] who laid the broad basic foundations of our modern knowledge of allergy and anaphylaxis To these important studies were soon

added a series of investigations in pathological anatomy and experimental pathology by Rossle[11] Frohlich[1], Gerlach[13] Klinge[14] Metz[15] Masugi[16 17] and others[18] who defined with more or less precision the anatomical characteristics of allergic states and of inflammatory reactions occurring in connection therewith

It was almost inevitable that these varied types of research should at last lead back toward clinical problems Gruber[19] appears to have been the first to suggest that periarteritis nodosa might represent the anatomical consequences of hyperergic reaction This hypothesis gained strength from a variety of clinical and pathological reports Thus Spiegel[0] in a detailed study of 17 verified cases observed that no less than 7 patients had had previous infections which without an intervening period of good health merged into symptoms attributable to periarteritis nodosa Spiegel further observed that prodromal illnesses such as infections or asthma had occurred in the majority of her cases Equally suggestive was the report by Clark and Kaplan[1] who described inflammatory arterial and periarterial lesions in two cases of serum disease Observations reported by Rackemann and Greene tended in the same direction These observers described 8 cases of periarteritis in persons afflicted with asthma and they found 19 additional examples of the same coincidence in the literature Confirmatory observations were reported by Blake[3] and by Dawson[4]

The next major contribution was made by Rich[5] who reported no less than 7 cases of periarteritis nodosa in persons who had received therapeutic sera or sulfonamides Six of the 7 had had reactions of hypersensitivity Rich astutely suggested that hypersensitivity of the anaphylactic and not of the tuberculin type might provide the etiologic clue to periarteritis nodosa This hypothesis he and his collaborators at once submitted to experimental trial[6]

The resultant observations will be summarized in later paragraphs of this review For purposes of historical analysis it is sufficient to record at this point that *lesions believed to be those of periarteritis nodosa were produced in rabbits subjected to experimental serum sickness These researches would place periarteritis nodosa in the category of diseases of allergy Confirmation will be needed*

The long chronicle of the history of periarteritis nodosa can now be summarized For many years the disease was little more than a rare curiosum of the pathology laboratory The complex and variable clinical manifestations usually misled the physician into erroneous diagnoses of

polyneuritis or nephritis, often he was betrayed into offering the diagnosis where the disease was absent Etiologic hypotheses wandered widely across the panorama of bacteriology and pathology Early in the twentieth century the new science of immunology evolved concepts of allergy and anaphylaxis which when brought into juxtaposition with accumulating clinical and pathological experience, gave rise to the hypothesis that periarteritis nodosa is an expression of the anaphylactic type of hypersensitivity This view prevails today While it leaves much still unexplained it offers the first satisfying approach to an explanation of the disease

Incidence

The incidence of periarteritis nodosa is of more than routine interest, inasmuch as certain peculiarities in the occurrence of the disease led to the experimental observations upon which the leading contemporary theory is based These peculiarities are (a) the fact that periarteritis nodosa sometimes occurs in persons who have had prolonged infections [7], (b) the tendency of the disease to occur in asthmatic persons [8] or after intractable urticaria (c) the frequent association of the disease with pronounced eosinophilia and (d) the emergence of periarteritis nodosa in persons who have had the anaphylactic type of hypersensitivity, especially after having received large doses of therapeutic sera [1] Periarteritis nodosa has also been observed to occur after the use of thiourea [9] thiouracil[30] sulfonamides[31, 32, 33] iodine[34] and arsenicals[35] under conditions suggesting that sensitivity to these drugs or to some altered protein produced by exposure to them is the determinant factor Correlations and recurring coincidences of this kind must be regarded as especially significant in view of the rarity of the disease

It has been known for decades that lesions almost indistinguishable from those of periarteritis nodosa occur in deer [36, 37] swine[38, 39], rats[40], and dogs[41] This consideration served at a comparatively early period to eliminate syphilis as a possible cause

The disease occurs at all ages including childhood[43, 44] and early infancy [4] Males are affected several times more often than females Cases have occurred in Negroes[46] and in Chinese[47] The disease is uncommon but by no means rare, Boyd[3] in 1938 estimated that 395 cases had been reported, these probably represent only a small fraction of the total number recognized by clinicians and pathologists

Etiology

In previous paragraphs it was shown that the introduction of the concepts of allergy and anaphylaxis and the anatomical analysis of allergic and anaphylactic inflammations led ultimately to the concept that periarteritis nodosa is a result of the anaphylactic type of hypersensitivity. The experimental evidence which supports this hypothesis was derived mainly from the work of Rich and Gregory[6, 45]. These investigators injected large doses of horse serum into rabbits and were able to reproduce a great part of the anatomical picture of periarteritis nodosa, i.e. edema, necrosis and hyalinization of the media accompanied by inflammatory infiltration in the media and in and around the adventitia of numerous blood vessels. Aneurysms were not produced. It was of particular interest that well developed lesions of periarteritis nodosa appeared even after a single large injection of serum in animals which were not previously sensitized. Long before the observations of these investigators lesions resembling those of periarteritis had been encountered in horses and other animals which had received repeated intravenous injections of bacterial cultures.

The researches of Rich and Gregory were confirmed by Hopps and Wissler[40] who found that large doses of horse serum given intravenously alone or in combination with orally administered sulfadiazine would produce arterial lesions in rabbits which were apparently identical with the lesions of periarteritis nodosa.

These studies of the consequences of anaphylactic hypersensitivity have provided the first clear insight into the possible pathogenesis of periarteritis nodosa. They by no means prove that hypersensitiveness is the sole cause of periarteritis or even that it is the usual cause. Such questions can be answered only by the diligent study of individual cases; this is difficult on account of the relative rarity of the disease and the even greater rarity of correct intra vitam diagnosis. The operation of anaphylaxis by no means negates the possibility that bacteria or their products also may be directly responsible for periarteritis nodosa. On the contrary, such a hypothesis makes it possible to implicate bacteria of diverse kinds. At all events it would be difficult to deny that the work of Rich and Gregory constitutes a valuable and impressive advance in our knowledge of the cause and pathogenesis of the disease.

The disease has been studied from a slightly different experimental angle by Smith, Zeel and McGuire[9]. These investigators enveloped the kidneys of rats and dogs in silk in order to produce hypertension

Periarteritis nodosa was found in 26 of 62 rats and 4 of 8 dogs which had been treated in this manner It is noteworthy that suppurative lesions were common in the perinephric tissues in their animals In humans with malignant hypertension however, pathologists frequently encounter cellular infiltrates in the adventitia and periarterial connective tissue adjacent to a necrotizing arteritis The finding of a periarteritic or even polyarteritic exudate is therefore, not necessarily to be accepted as evidence of allergy or anaphylaxis or of the disease periarteritis nodosa

Pathology

Periarteritis nodosa may be defined anatomically as an inflammatory disease of medium sized and small arteries frequently accompanied by necrosis of the vessel wall The lesion apparently begins in the media especially in that part which is immediately subjacent to the intima The earliest discernible change is a slight degree of thickening due to edema Very early the affected part of the media develops a structureless hyaline appearance or shows increased avidity for eosin in consequence of this it appears as a heavily stained pink homogeneous layer This abnormal appearance quite often fails to extend entirely around the vessel The media thus altered tends to resemble fibrin and the name 'fibrinoid change or fibrinoid degeneration has been employed for this reason At the same time as was clearly shown by Fishberg [1], threads of genuine fibrin can sometimes be demonstrated in the media by the use of special techniques The deposition of fibrin apparently begins in the immediate vicinity of the internal elastic lamella While the media may contain the cellular components of an inflammatory exudate these are most abundant in the adventitia and in tissues surrounding the adventitia Such cellular infiltrates are commonly dense and conspicuous Mononuclear cell types usually predominate but not to the exclusion of polymorphonuclear leukocytes Eosinophilic cells are often present, but this is not an invariable rule Plasma cells occur rarely The intima may be unaltered or may show endothelial proliferation with consequent narrowing of the lumen

Quite often the elastic and muscular tissue of the media is fragmented or destroyed Where necrosis has been extensive all trace of medial structure may vanish Most commonly this extensive alteration is limited to a sector of the affected vessel

In vessels affected by these processes a number of complications may

ensue Localized enfeeblement of the arterial wall may later result in the formation of aneurysms it should be emphasized that this takes place in a minority of cases As might be expected these aneurysms occasionally rupture producing hemorrhage which often proves fatal or hematomata The rupture of a small abdominal aneurysm or of a vessel which is diseased but *not aneurysmal*[6] *is one of the common causes of* death in periarteritis nodosa Another sequel is thrombosis which may occur in an affected vessel whether an aneurysm has formed or not As in other cases thrombosis is followed by infarction and often by recanalization

Cases of long duration may exhibit evidences of healing [37 5] The cellular exudates resorb and are replaced by fibroblasts Rarely giant cells of the Langhans type are found[53] Ultimately a mature connective tissue develops in and around the diseased vessel and the lumen may be occupied either by recanalized thrombi or by small granulomata The lumen need not be obstructed but may be somewhat reduced in consequence of thickening of the intima

It might be expected that a disease which produces alterations as severe and as extensive as those which have been described would necessarily betray itself to the naked eye by conspicuous gross lesions Such is not always the case In many instances little or nothing abnormal can be seen grossly at autopsy On occasion the muscles may show small gray flecks which represent relatively large perivascular exudates In more favorable instances and these are the minority nodules from 2 to 10 or more millimeters in diameter are found on arteries These are encountered most often in the mesentery especially near the attachment of the intestine or beneath the capsules of the solid viscera of the abdomen A favorite location is the gallbladder[54] especially near the origin of the cystic vessels Most conspicuous are the aneurysms which occur along the coronary arteries these are commonly multiple and quite often are unaccompanied by evidence of myocardial necrosis Aneurysms may occur along the pelvic vessels where they are readily overlooked and in the renal or intrarenal arteries Aneurysms infarcts and hemorrhages may be found in the testes While the mesenteric intestinal coronary renal and splenic arteries are most commonly affected lesions have also been reported in the hepatic cerebral suprarenal internal mammary intercostal phrenic and thyroid[55] arteries Hemorrhages infarcts and scars show a correspondingly wide distribution Indeed one of the minor characteristics of periarteritis nodosa is the occurrence of infarcts in un

common localities e g the testis the pancreas, and the peripheral nerves Very often a diseased vessel situated superficially in a solid viscus under goes rupture with resultant formation of a subcapsular hematoma Such subcapsular hematomata are highly characteristic of periarteritis nodosa

It now remains to consider the special anatomical peculiarities which the disease exhibits in various organs, systems or regions

In view of the prominence of myalgia and atrophy in the clinical picture of periarteritis nodosa it is a little astonishing to find that the literature is poor in detailed studies of the lesions in muscles The small blood vessels in these organs exhibit the typical alterations which have already been discussed In one case described by Wohlwill[5] the muscles had undergone severe degeneration Many of the fibers were swollen many atypically Many were devoid of striation and were split into fragments Others had atrophied The sarcolemma nuclei had undergone multiplication or pyknosis, while the interstitial tissues had proliferated Since these lesions are of degenerative and not of inflammatory nature, the term myositis would be inapplicable The true nature of the process can be recognized in these instances when the characteristic arteritis is observed in the interstitial vessels of the musculature

While it is well recognized that the peripheral nerves are frequently and conspicuously involved there is no unanimity as to the pathogenesis of such involvement In severe cases the nerves show hemorrhages necroses or even infarcts[58] Myelin sheaths and axis cylinders deteriorate and may disappear and the nerve tissue becomes invaded by glia It is usual for the severity and extent of the process to differ in different nerves Probably these alterations are to be ascribed to lesions of the fine blood vessels with which nerves are supplied In cases which have been examined with adequate thoroughness these vessels show the medial and adventitial lesions which have been described above The lesion at a given level of a peripheral nerve is often found to correspond to a vascular lesion situated at a more proximal level neglect of this simple principle is the cause of some of the confusion in the literature Kernohan and Woltman [9] concluded from their meticulous study that lesions in the nerves are solely the result of inadequate blood supply In one of the cases reported by these authors the periarteritis nodosa was limited to the nerve trunks of the upper and lower limbs Careful examination of all the other organs of the body failed to reveal a single vascular lesion except in one artery in the capsule of the prostate

Lesions have also been encountered in the brain and in the basilar and

spinal meninges[60] but not very frequently Encephalomalacia[5] and cerebral infarction have been reported[61]

Much more worthy of note are the ocular lesions These are peculiar in distribution inasmuch as the arteries of the ciliary system[6, 63] and the choroidal vessels[64] tend to be affected predominantly Involvement of the retinal arteries would seem to be less common although in one instance[65] a fusiform aneurysm was found ophthalmoscopically in a branch of the retinal artery For the most part the lesions in the ocular vessels do not differ inherently from those found elsewhere in the body The local consequences however are complicated Perivascular infiltrates for example may displace choroidal pigment along the long axis of the choroid Hemorrhage and necrosis may occur in the choroid granular exudates may appear in the subretinal space and the rods and cones may disintegrate Severe periarteritic involvement of the kidneys is commonly followed by albuminuric retinitis papilledema and optic atrophy

Special attention must be given to the renal lesions of periarteritis nodosa since renal involvement is extremely common although not invariable In an apparently unique case reported by Fishberg[42] the kidneys were the only organs involved In two cases of periarteritis nodosa reported by Otani[66] the kidneys were virtually devoid of lesions of that disease but showed instead the picture of malignant nephrosclerosis The commonest renal lesions are aneurysm unruptured or ruptured of the *renal arteries or their intrarenal branches*[67] *thrombosis of major arterial* branches with infarction perinephric hematoma or hemorrhage and various types of glomerulonephritis The complexity or obscurity of the lesion often deceive the internist and surgeon alike In patients who recover from the inflammatory stage of the disease and enter a prolonged remission death may later supervene from renal insufficiency resulting from the ischemic reduction in renal parenchyma

Symptoms and Clinical Course

In the preceding section it was shown that the comparatively simple arterial lesion of periarteritis nodosa could occur in almost any part of the body Hence it comes about that a great variety of clinical symptoms is produced While this variation has in the majority of cases prevented clinicians from arriving at a correct diagnosis during the lifetime of the patient it is necessary for purposes of description to seek and to stress whatever elements of uniformity or regularity can be derived from

common localities e g the testis the pancreas and the peripheral nerves Very often a diseased vessel situated superficially in a solid viscus undergoes rupture with resultant formation of a subcapsular hematoma Such subcapsular hematomata are highly characteristic of periarteritis nodosa

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Lesions have also been encountered in the brain and in the basilar and

The skin and subcutaneous tissues may bear the brunt of the symptoms[74]. Purpura, petechiae, ulcers, urticaria, erythema nodosum and erythema multiforme have been observed in cases of periarteritis nodosa. Occasionally areas of skin and subcutaneous tissue become necrotic; digits may become gangrenous[44]. Circumscribed edemas[75, 76] have been described. These usually occur on the limbs, especially on the extensor surfaces of the arm, and may omit the periarticular regions. Conversely, periarthritis or arthritis may be present.

Several authors have reported the presence of livedo reticularis or livedo racemosa[77, 44, 78]. This consists of a conspicuous branching system of red or purple markings which appear on the nates and the extremities. The central trunk may be palpable as an elevated ridge. Ketron has shown that the lesion consists of dilated and engorged small blood vessels in the superficial strata of an edematous cutis, associated with thrombosis and leukocytic infiltration of the deeper vessels.

It is generally agreed that subcutaneous nodules occur in a minority of cases of periarteritis nodosa. These lesions are usually from 1 to 5 mm in diameter; the occurrence of hemorrhage may convert a small nodule into a firm or boggy mass. The nodules are mobile and often tender, but the tenderness may be temporary. They may pulsate. The overlying skin is usually normal but may be erythematous. The nodules occur most commonly on the extensor surfaces of the extremities, along the temporal arteries, and on the trunk. At times they occur on almost any part of the body, even the tongue. It is certainly significant that the nodules tend to appear in crops. They sometimes vanish in a few days. More often they shrink slowly; occasionally they persist. It is generally believed that when nodules are numerous the disease runs a protracted or benign course[79], but this has not been the authors' experience.

Neural and muscular symptoms are relatively common in periarteritis nodosa and have often led to the incorrect and incomplete diagnosis of polyneuritis or myositis. Most often pains of moderate or great intensity occur and recur in the extremities. Involvement is usually multiple and asymmetrical. The affected muscle groups are tender, at times spastic or nodular. The rupture of a small aneurysm occasionally gives rise to a more massive lesion consisting chiefly of hematoma. In severe cases the affected muscle groups tend to atrophy. Periarteritic disease of peripheral nerves produces weakness, palsy, areflexia and anesthesia. The median, ulnar, radial, tibial and peroneal nerves are most commonly

clinical experience and from a study of the literature In this connection the most helpful recent reviews are those of Spiegel[0] Boyd[3, 68] Middleton and McCarter[69] and Weiss[70]

It was traditional in the older literature to describe the clinical picture of periarteritis nodosa as a triad consisting of chlorotic marasmus, polyneuritis and abdominal symptoms A fourth component, nephritis was added later This abbreviated summary of the disease scarcely suggests the bewildering complexity of the symptoms and it omits one important element, i e fever

In an appreciable proportion of cases periarteritis nodosa develops imperceptibly from a prodromal illness of infectious or allergic nature, especially asthma intractable urticaria severe prolonged sinusitis, scarlet fever[71], or rheumatic fever[7] The prodromal febrile disease proves to be unusually tenacious and becomes complicated by exceptional symptoms such as myalgia weakness of a muscle group, abdominal pain, hematuria or purpura More often no prodrome occurs or none is recognized and the disease makes its appearance as a fever of unknown origin This fever is often labeled vaguely and inaccurately, as septic It is commonly of moderate or great intensity and is not accompanied by chills by regular elevations or by enlargement of the spleen If cardiac murmurs or arthralgia are present the diagnosis of rheumatic fever may be made The latter disease in fact sometimes appears concurrently with periarteritis nodosa as the studies of Friedberg and Gross[7] have shown If purpura and anemia are found or if evidence of visceral infarction has appeared the diagnosis of bacterial endocarditis is apt to be offered Blood cultures however are negative and sooner or later the picture is further diversified by such features as arthralgia myalgia, albuminuria microscopic hematuria arterial hypertension or azotemia In still another type of case an apparently normal person is stricken by an acute surgical crisis[73] and an inflamed or infarcted viscus usually the appendix gallbladder or kidney is removed In such cases the diagnosis is made by the pathologist and received with surprise by the clinician Occasionally in cases of this type the illness apparently ceases with excision of the diseased organ More often it progresses to a fatal end

These examples will serve to describe in a very general way some of the outstanding clinical characteristics of the disease In any one case the preponderance of clinical symptoms may affect one organ or one area For this reason it is convenient to distinguish a number of more or less arbitrarily established clinical forms

The skin and subcutaneous tissues may bear the brunt of the symptoms[74] Purpura petechiae ulcers urticaria erythema nodosum and erythema multiforme have been observed in cases of periarteritis nodosa Occasionally areas of skin and subcutaneous tissue become necrotic digits may become gangrenous[41] Circumscribed edemas[5 76] have been described These usually occur on the limbs especially on the extensor surfaces of the arm and may omit the periarticular regions Conversely periarthritis or arthritis may be present

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Neural and muscular symptoms are relatively common in periarteritis nodosa and have often led to the incorrect and incomplete diagnosis of polyneuritis or myositis Most often pains of moderate or great intensity occur and recur in the extremities Involvement is usually multiple and asymmetrical The affected muscle groups are tender at times spastic or nodular The rupture of a small aneurysm occasionally gives rise to a more massive lesion consisting chiefly of hematoma In severe cases the affected muscle groups tend to atrophy Periarteritic disease of peripheral nerves produces weakness palsy areflexia and anesthesia The median ulnar radial tibial and peroneal nerves are most commonly

affected[81] In some cases the damage is limited to a single nerve, but more commonly the nerve damage is bilateral and asymmetrical Reference has already been made to a case of Kernohan and Woltman[59] in which lesions were virtually limited to the nerves and their nutrient vessels Occasionally the clinical signs of neural damage regress and recur Cerebral signs and symptoms are rare, probably the commonest are hemiplegia and convulsions

With regard to its effect on the eyes, periarteritis nodosa has been studied more thoroughly by pathologists than by clinicians It has already been stated that the disease affects the ciliary and choroidal vessels more often than the retinal The commonest ophthalmoscopic picture is that of albuminuric retinitis, including papilledema hemorrhages, and exudates Uveitis[8] and episcleritis have been reported In an apparently unique case described by Goldsmith[6] a small aneurysm was visible on a branch of the central retinal artery Goldstein and Wexler[6] have reported a case of bilateral atrophy of the optic nerve Gibson and Quinlan [9] have reported a case of thrombosis of the central artery of the retina

Many cases of periarteritis nodosa present symptoms referable to the abdominal viscera Frequently there are attacks of abdominal pain which may simulate the symptoms of an acute surgical condition especially cholecystitis appendicitis, intestinal perforation, and pancreatitis Laparotomy may reveal necrosis gangrene or perforation of a viscus, or intraperitoneal hemorrhage or a hematoma situated in the retroperitoneal tissues or beneath the capsule of the liver or kidney Laparotomy may also reveal no gross lesion adequate to account for the symptoms, this is not surprising since it is well known that gross lesions may be entirely absent even at autopsy

Of passing interest is the fact that lesions of the pancreas are relatively common These include infarction, hemorrhage, and fibrosis It is equally interesting as Boyd[83] correctly observes that diabetes mellitus rarely occurs in conjunction with periarteritis nodosa

Another discrepancy between anatomical and clinical findings refers to the heart It has been observed repeatedly that the major coronary vessels may be studded with aneurysms in the absence of angina pectoris or myocardial insufficiency The complete anatomical and clinical picture of coronary thrombosis occasionally supervenes however In other cases there are uncharacteristic murmurs which may lead to an erroneous diagnosis of bacterial endocarditis especially since fever is rarely absent

Hypertension is common early in the disease and also appears later as a concomitant of renal involvement

The kidneys in fact are affected in almost every case of periarteritis nodosa The clinical appearances may be those of acute or chronic glomerulonephritis malignant nephrosclerosis renal infarction or renal colic Uremia is common The combination of any form of renal disease with symptoms of arthritis or peripheral neuritis should lead to a surmise of periarteritis nodosa especially if fever has been present

The testes are prone to be involved the patient usually complaining of the pain and tenderness produced by hemorrhages or infarcts While it is not rare for microscopic lesions of periarteritis nodosa to occur in the female internal genitalia no distinctive clinical signs are known

It is usually found that the lungs escape gross involvement in periarteritis nodosa apart from the fact that asthma is a common prodrome or concomitant Elkeles and Glynn[84] however have found roentgen evidence of transient pulmonary infiltration and persistent or progressive development of changes in the hilar regions and bases

Such is the clinical picture of periarteritis nodosa as it affects the various organs systems and regions in the more typical cases The physician will understand that the symptoms mentioned may appear in almost any combination that almost any group of symptoms may dominate in any one case and that the disease may progress with any degree of celerity or slowness It is generally believed that when subcutaneous nodules are numerous the course is slow and mild but this may be because the aneurysmal nodules are a late manifestation of the subacute variety of the disease In occasional instances[7] the arterial lesions are found to have healed but death ensues because of irreparable visceral damage especially contraction of the kidneys A few patients recover completely It may be predicted that the more frequent use of biopsy will reveal numbers of mild cases which now escape detection

Diagnosis

With respect to diagnosis periarteritis nodosa is the blackest of clinical *betes noires* While the medical literature contains many proud reports of cases successfully detected it scarcely suggests the even larger number of cases in which the diagnosis of periarteritis nodosa was made and later proved to be incorrect Probably every seasoned clinician has had this experience

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bacterial endocarditis Great reliance naturally will be placed on bacteriological studies especially cultures of blood and sputum The presence of polyneuritic pain arthralgia polymorphous cutaneous eruptions eosinophilia and asthma favor the diagnosis of periarteritis nodosa The occurrence of chills splenomegaly persistent or increasing pulmonary infiltrations and white centered *petechiae point away from periarteritis nodosa*

The occurrence of acute rheumatic fever is equivocal since this disease occurs independently of periarteritis as well as in association with it

Difficulty may be encountered in distinguishing periarteritis nodosa from temporal arteritis especially inasmuch as the latter disease may be accompanied by prolonged fever wasting and pain Since even biopsy may be inconclusive the decision must occasionally be made according to the preponderance of evidence Temporal arteritis usually occurs in middle aged or elderly persons especially women Not only are the *temporal arteries painful and tender but the overlying tissues are apt* to be red and swollen Since numerous branches of the external carotid artery may be involved the clinical picture may be that of polyarteritis Constitutional symptoms such as fever weakness anorexia and loss of *weight occur in most cases Ocular symptoms are common and pain on* mastication is characteristic In well marked cases an involved vessel shows intimal hyperplasia and medial necrosis associated with the formation of a granulomatous tissue which frequently contains giant cells A periarterial exudate is often present Aneurysms are rare more commonly the temporal arteries contain one or more tender nodules which are caused usually by localized inflammation unaccompanied by aneurysmal dilatation Involvement of the brain and eye have been reported indeed blindness is a relatively common complication Rare cases manifesting visceral involvement are difficult to distinguish from cases of periarteritis nodosa

Unlike *in generalized periarteritis eosinophilia and an association* with asthma urticaria or other allergic phenomena are rarely noted The arterial lesions in the microscopic sections of biopsied material appear to be much more granulomatous and characteristically contain more multinucleated *giant cells than in periarteritis nodosa In this respect the pathological* process more closely approximates that observed in early lesions of thrombo angiitis obliterans (Buerger)

The prognosis in temporal arteritis is far better than in generalized

In periarteritis nodosa as in many other elusive maladies the first diagnostic act is to suspect the presence of the disease The more common combinations of symptoms have already been described and need not be repeated here The variety of systems and organs involved in the clinical picture should arouse suspicion Occasional help is obtained by examination of the blood Moderate hypochromic anemia is usual Leukocytosis is common and at times exceeds 20 000 per cu mm Pronounced eosinophilia is present in more than half the cases at some stage of the disease, it is most apt to be encountered when asthma or urticaria is present Eosinophiles may at times constitute more than 65 per cent of the circulating leukocytes at some stages of the disease and in some patients throughout the course of the disease eosinophilia may be absent The occurrence of azotemia albuminuria hematuria, and arterial hypertension provides valuable supporting evidence Transient pains in muscles abdomen or thorax also focus attention on the wide dissemination of the disease process and implant suspicion of widely distributed vascular lesions

The most useful diagnostic procedure is biopsy This should include skin subcutaneous tissues and fragments of muscle While the sites of nodules or other lesions are to be selected preferentially, positive evidence of the disease may be obtained even from areas which appear grossly normal The microscopic examination of tissues excised at surgical operations should of course be performed with care, special attention being given to blood vessels

As recent research has confirmed the opinion that periarteritis nodosa is frequently a consequence of hypersensitivity, investigations into the allergic condition of the patient may at times prove diagnostically useful It will be clear from facts already given that periarteritis nodosa and trichiniasis are apt to be mistaken for one another Indeed the diagnosis of trichiniasis was considered in the classic case of Kussmaul and Maier In favor of trichiniasis are abrupt simultaneous onset of fever and myalgia in a previously healthy person absence of renal and abdominal signs and symptoms absence of cutaneous lesions In favor of periarteritis are evidence of asthma or other allergic disorders insidious onset hypertension prolonged course visceral complications microscopic hematuria skin lesions The difficulty is usually resolved by biopsy of muscle tissue

It is not rare for cases of periarteritis nodosa to camouflage themselves as fevers of unknown origin The clinician is then called upon to rule out such diseases as typhoid fever miliary tuberculosis brucellosis and

the disease characterized by eosinophilia and by migratory pulmonary infiltrations (Loeffler s pneumonia) the response may be particularly striking The characteristic roentgenographic shadows may disappear within 48 to 72 hours

To maintain the clinical improvement therapy must usually be continued on a varying maintenance level for many months — in fact indefinitely if the disease does not undergo spontaneous remission

The results of treatment with cortisone hydrocortisone metacortone and corticotropin are far less favorable in periarteritis nodosa than in some of the other collagen diseases such as acute rheumatic fever rheumatoid arthritis and disseminated lupus erythematosus Often extensive vascular involvement of the heart and kidneys occurs early in the disease and such lesions are largely irreversible Their effect upon the parenchyma of these vital organs leads ultimately to death in uremia or circulatory failure despite the suppression of other clinical manifestations The polyneuritic symptoms are similarly resistant to treatment

Cortisone and corticotropin are equally effective in most cases the latter being about twice as potent An occasional patient may prove resistant to cortisone but may respond to corticotropin The advantage of cortisone metacortone and hydrocortisone is that they may be administered orally The use of these hormonal agents is contraindicated in the presence of functional impairment of the heart and kidneys because of their untoward effects upon body water and electrolytes

The usual starting dosages are 150 to 50 mg of cortisone or 60 to 80 mg of metacortone per day administered by mouth in four equally divided doses When corticotropin is used the usual starting dose is 100 units per day divided into four intramuscular injections For critically ill patients daily dosages as high as 500 mg of cortisone or 300 units of corticotropin in divided doses have been required

While the patient is under intensive therapy the body weight should be measured daily a low sodium diet should be taken and adequate amounts of potassium chloride (4 to 8 gm per day) should be given to prevent hypokalemia and hypochloremic alkalosis[65]

After the clinical manifestations of the disease have been under complete control for 10 days to weeks the dosage should be reduced gradually until the minimum daily amount required for the maintenance of complete clinical remission is determined Serious relapse is less likely while under treatment if the dosage is reduced very slowly over a period of several months Each case will respond differently but it is usually

periarteritis probably because of the limited distribution of the arterial disease and the usual absence of visceral involvement Headache is one of the most conspicuous symptoms It is sometimes relieved promptly by excision of a nodule on a temporal artery and by ligation of the vessel Most persons with this disease recover spontaneously after months of illness

TREATMENT

With respect to treatment our knowledge of periarteritis nodosa is at its weakest Little can be offered except symptomatic relief as the need arises or changes As in any chronic disease encouragement may alleviate suffering and prolong life It should be emphasized that many pass into a temporary remission and some recover A search should be made for hypersensitiveness especially to foods and drugs Antihistaminic drugs such as pyribenzamine and benadryl should be employed, although in most instances they have proved to be therapeutically ineffective The use of sulfonamides and iodides should be avoided The diet should be adapted to the requirements and desires of the patient In the present enthusiasm for supplementary vitamins the need for calories should not be overlooked Antibiotics such as penicillin and streptomycin are usually of no therapeutic value Physiotherapy should be employed for the relief of pain in the muscles and for the prevention of atrophies and contractures Large amounts of salicylates in doses comparable to those employed in acute rheumatic fever 1½ to 2 gm (gr 90 to 120) a day may give symptomatic relief and may even reduce the inflammatory manifestations Uremia should be palliated in the usual manner by a diet consisting essentially of carbohydrate foods and containing the minimum amount of protein

As in other collagen diseases cortisone hydrocortisone metacortone, and corticotropin (ACTH) in adequate doses may be dramatically effective in controlling clinical manifestations in spite of the fact that they are not curative Therapy with these hormones prolongs life by controlling hyperergy and reducing the reactive process in the affected vascular tissues until the actively destructive stage of the disease has run its course and the disease spontaneously enters a stage of remission

Fever is usually promptly controlled and if present joint and muscle pains and a multitude of allergic skin reactions are favorably affected Often new vascular lesions fail to appear as long as the patient is under the full influence of the hormones In the presumably allergic form of

the disease characterized by eosinophilia and by migratory pulmonary infiltrations (Loeffler's pneumonia) the response may be particularly striking The characteristic roentgenographic shadows may disappear within 48 to 72 hours

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best to reduce the daily dosage by 5 or 10 mg of cortisone at intervals of not less than three or four days Such fine adjustment of dosage may be facilitated by the use of 5 mg tablets of hydrocortisone or meta cortone

When corticotropin is employed and the minimum daily maintenance dose has finally been determined, a long-acting corticotropin gel may be substituted during continued maintenance therapy A single daily injection of this gel may afford a beneficial effect on the disease for at least 24 hours

The major objective of hormonal therapy is to determine the main tenance dosage of cortisone or corticotropin which will provide maxi mum freedom from troublesome symptoms compatible with minimal disturbance from undesired effects of the hormone As the untoward effects of these potent therapeutic agents may be serious or even disas trous, patients should be under treatment in a hospital The reader is referred to other sections of the *Oxford Loose Leaf Medicine* for a more detailed description of the hazards of cortisone and corticotropin therapy or to *Medical Uses of Cortisone* by Lukens *et al*[86]

BIBLIOGRAPHY

1 KUSSMAUL A and MAIER R Uber eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeines Muskellahm ung einhergeht Deutsch Arch f klin Med 1866 I 484

2 ROKITANSKY C F Aneurysmenbildung samtliche Arterien mit Aus nahme die Aorta und der meisten ansehnliche primitive Aeste der selbe ferner mit Ausnahme der Gehirnarterien Denkschrft d k Akad d Wissensch Wien 185 IV 49

3 BOYD L J I The clinical aspects of periarteritis nodosa Bull N Y Med Coll and Flower and Fifth Ave Hosp 1938 I 219

4 VON HANN F Patho histologische und experimentelle Unter suchungen uber Periarteritis nodosa Virch Arch f path Anat u Physiol 19 0 CCXXVII 90

5 HART K Die Meso Periarteriitis (Periarteriitis nodosa) Berl klin Wochnschr 1908 XLV 1305

6 KLOTZ O Periarteritis nodosa Jour Med Res 1917 XXXVII (n s vol XXXII) 1

7 MANGES M and BAEHR G Periarteritis nodosa Am Jour Med Sci 19 1 CLXII 16

8 PIRQUET C P Klinische Studien uber Vakzination und vakzinale Allergie F Deuticke Leipzig 1907
9 ARTHUS N M Injections repetees de serum de cheval chez le lapin comptes rendus d Soc de Biol 1903 LV 817
10 RICHET C De l anaphylaxie et des toxogenines Ann Inst Pasteur 1908 XXII 465
11 ROSSLE R Über die Merkmale der Entzundung in Allergischen Organismus Verhandl d Deutsch pathol Ges 1914 XVII 81
1 FRÖHLICH A Über lokale gewebliche Anaphylaxie Inaug Diss Jena 1914
13 GERLACH W Studien uber hypergergische Entzundung Virch Arch f path Anat u Physiol 1943 CCXLVII 94
14 KLINGE F Der Rheumatismus Ergebn d allg Path u path Anat (Lubarsch Ostertag) 1933 XXVII 1
15 METZ W Die geweblichen Reaktionserscheinungen an der Gefass wand bei hyperergischen Zustanden und deren Beziehungen zur Periarteritis nodosa Beitr z path Anat u z allg Path 1931 LXXXVIII 17
16 MASUGI M and ISIBASI T Über allergische Vorgange bei Allgemeininfektion vom Standpunkt der experimentellen Forschung zu gleich ein Beitrag zur Pathogenese der diffusen glomerulonephritis und Periarteritis nodosa Beitr z path Anat u z allg Path 1936 XCVI 391
17 MASUGI M and SATO Y Über die allergische Gewebsreaktion der Niere zugleich ein experimenteller Beitrag zur Pathogenese der diffusen glomerulonephritis und der Periarteritis nodosa Virch Arch f path Anat u Physiol 1934 CCXCIII 615
18 KNEPPER R Über die Lokalisierung der experimentellen allergischen Hypergergie Virch Arch f path Anat u Physiol 1935 CCXCVI 364
19 GRUBER G B Über die Pathologie der Periarteritis nodosa (Kussmaul Maier) Zentralbl f Herz u Gefasskrankh 1917 IX 45 and 69
o SPIEGEL R Clinical aspects of periarteritis nodosa Arch Int Med 1936 LVIII 993
1 CLARKE, E and KAPLAN B I Endocardial arterial and other mesenchymal alterations associated with serum disease in man Arch Path 1937 XXIV 458
22 RACKEMANN R M and GREENE, J E Periarteritis nodosa and asthma Transact Assoc Am Phys 1939 LIV 11
3 BLAKE F G ibid p 118
4 DAWSON M H ibid p 118
25 RICH A R The role of hypersensitivity in periarteritis nodosa as indi

cated bv 7 cases developing during serum sickness and sulfonamide therapy Bull Johns Hopkins Hosp 1940 LXXI 123
-6 RICH A R and GREGORY J E Experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity Bull Johns Hopkins Hosp 1943 LXXII 65
7 KLINGER H Grenzformen der Periarteritis nodosa Frankfurt Zeitschr f Path 1931 XLII 455
8 COHEN M B and YOUNG A M The clinical diagnosis of periarteritis nodosa Jour Am Med Assoc 1936 CVII 1555
9 GIBSON P C and QUINLAN J T Periarteritis nodosa in thiourea therapy Lancet 1945 II 108
30 MARINE D and BAUMANN E J Periarteritis nodosa like lesions in rats fed thiouracil Arch Path 1945 XXXIX, 3-5
31 LICHTENSTEIN L and FOX L Necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following administration of sulfathiazole report of case Am Jour Path 1946 XXII 66,
3- RICH A R Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa another case associated with a sulfonamide reaction Bull Johns Hopkins Hosp 194 LXXI 375
33 ROSENAK B D and MASCHMEYER R H Periarteritis nodosa possibly due to sulphadiazine sensitivity Lancet 1945 I 305
34 RICH A R Hypersensitivity to iodine as a cause of periarteritis nodosa Bull Johns Hopkins Hosp 1945 LXXVII 43
35 MILLER H G and NELSON M G Polyarteritis nodosa developing during antisyphilitic treatment Lancet 1945 II -00
36 LUPKE F Ueber Periarteritis nodosa bei Axishirschen Verhandl d Deutsch pathol Gespzkh Jena 1907 p 149
37 JAGER F Zur histologischen Ausheilung der Periarteritis nodosa und deren Beziehung zur juvenilen Atherosclerose Virch Arch f path Anat u Physiol 1933 CCLXXXVIII 833
38 JOEST E and HARZER J Ueber Periarteritis nodosa beim Schwein Beitr z path Anat u z allg Path 19 I LXIX 85
39 NIEBERLE K Zur Kenntnis der Periarteritis nodosa bei Tieren Virch Arch f path Anat u Physiol 19 5 CCLVI 131
40 WILENS S L and SPROUL E E Spontaneous cardiovascular disease in the rat II Lesions of the vascular system Am Jour Path 1938 XIV 01
41 BALO J Periarteritis nodosa beim Hunde und vergleichende Untersuchungen uber diese Erkrankung bei Menschen und Hunde, Virch Arch f path Anat u Physiol 1924 CCXLVIII 337

4 SCALA G La periarterite nodosa nell uomo e negli animali Folia Med 1927 XIII 1170
43 ROTHSTEIN J L and WELT S Periarteritis nodosa in infancy and childhood Am Jour Dis Child 1933 XLV 1 77
44 GALAN E Periarteritis Nodosa Bol de la Soc Cubana de Pediatria 1945 XVII 93
45 WILMER H A Two cases of periarteritis nodosa occurring in the first month of life Bull Johns Hopkins Hosp 1945 LXXVII 75
46 WEBB A C Periarteritis nodosa in pregnancy Arch Path 1944 XXXVIII 3 9
47 CONTRATTO A W Periarteritis nodosa A report of two cases one with special reference to sensitivity factors Arch Int Med 1947 LXXX 567
48 RICH A R and GREGORY J E Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity Bull Johns Hopkins Hosp 1943 LXXIII 39
49 HOPPS H C and WISSLER R W The experimental production of generalized arteritis and periarteritis (periarteritis nodosa) Jour Lab and Clin Med 1946 XXXI 939
50 SMITH C C ZEEK P M and McGUIRE J Periarteritis nodosa in experimental hypertensive rats and dogs Am Jour Path 1944 XX 7 1
51 FISHBERG A Zur Kenntnis der Periarteriitis nodosa insbesondere der Histiopathogenese Virch Arch f path Anat u Physiol 19 3 CCXL 483
5 LINDSAY S AGGELER P M and LUCIA S P Chronic granuloma associated with periarteritis nodosa report of case associated with renal failure Am Jour Path 1944 XX 1057
53 KRAHULIK L ROSENTHAL M and LOUGHLIN E Periarteritis nodosa (necrotizing panarteritis) in childhood with meningeal involvement Am Jour Med Sci 1935 CXC 308
54 GRAF L Ueber einen Fall von Periarteriitis nodosa mit multipler Aneurysmabildung Beitr z pathol Anat u z allg Pathol 1896 XIX 181
55 JORES L Arterien Henke F and Lubarsch O Handbuch der Speziellen Pathologischen Anatomie und Histologie vol Springer Berlin 19 4 608 786
56 BALO J Ueber die Ursache der im Verlaufe der Periarteriitis nodosa vorkommenden Polyneuritiden Zeitschr f d ges Neurol u Psychiat 1931 CXXXIV 71
57 WOHLWILL F Uber die nur mikroskopisch erkennbare Form der

Periarteritis nodosa Virch Arch f Path Anat u Physiol 19 3 CCXLVI 377
58 KULKOW A E Zur klinischen Diagnose und Pathogenese der poly-neuritischen Form von Periarteritis nodosa Acta Med Scandinav 1941 CVIII 586
59 KERNOHAN J W and WOLTMAN H W Periarteritis nodosa a clinicopathologic study with special reference to the nervous system Arch Neur and Psych 1938 XXXIX 655
60 HORANYI B and BOSZORMENYI G Polyneuritiden bei Periarteritis nodosa Zentralbl f d Ges Neurol u Psych 1937 LXXXVII 4 4
61 DIAZ RIVERA R S and MILLER A J Periarteritis nodosa clinicopathological analysis of 7 cases Ann Int Med 1946 XXIV 420
6 GOLDSTEIN I and WEXLER D Bilateral atrophy of the optic nerve in periarteritis nodosa a microscopic study Arch Ophth 1937 XVIII 767
63 VON HERRENSCHWAND F Ueber morphologische Befunde am Auge bei Periarteritis nodosa im Vergleich zu denen bei Sepsis lenta Klin Monatsbl f Augenheilk 19 9 LXXXIII 419
64 GOLDSTEIN I and WEXLER D The ocular pathology of periarteritis nodosa Arch Ophth 19 9 II 88
65 GOLDSMITH J Periarteritis nodosa with involvement of choroidal and retinal arteries Am Jour Ophth 1946 XXXIX 435
66 OTANI S Malignant nephrosclerosis and periarteritis nodosa Arch Path 1933 XVI 435
67 HERBUT P A and PRICE A H Periarteritis nodosa producing aneurysm of the renal artery and hypertension Arch Path 1945 XXXIX 74
68 BOYD L J II Clinical aspects of periarteritis nodosa Bull N Y Med Coll Flower and Fifth Ave Hosps 1940 III 3
69 MIDDLETON W S and McCARTER J C The diagnosis of periarteritis nodosa Am Jour Med Sci 1935 CXC 91
70 WEISS S Arteritis diseases associated with inflammatory lesions of the peripheral arteries New England Jour Med 1941 CCXXV 579
71 PEALE A R GILDERSLEEVE N and LUCCHESI P F Periarteritis nodosa complicating scarlet fever Am Jour Dis Child 1946 LXXII 310
7- FRIEDBERG C K and GROSS L Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease Arch Int Med 1934 LIV 170
73 SPALDING J E Periarteritis nodosa and its surgical significance, Guy s Hosp Rep 1940 41 XC 234

74 BOYD L III Periarteritis nodosa Cutaneous symptoms Bull N Y Med Coll Flower and Fifth Ave Hosps 1940 III 175
75 VESZPREMI D Uber die Periarteritis nodosa Beitrag z path Anat. u z allg Path 191 LII 476
76 MACKEITH R Localized subcutaneous oedema with weakness of limb muscles a syndrome due to polyarteritis nodosa Brit Med Jour 1944 I 139
77 KETRON L W *Cutaneous manifestations of periarteritis nodosa* Arch Dermat and Syph 1939 XL 9 9
78 CAROL W and PRAKKEN J R Die kutane Form der Periarteritis nodosa *Acta Dermat—Venereol 1937 XVIII 10*
79 LINDBERG K Ein Beitrag zur Kenntnis der Periarteritis nodosa Acta Med Scandinav 1931 LXXVI 183
80 LINDBERG K *Ueber eine subkutane Form der Periarteritis nodosa* mit langwierigem Verlauf Acta Med Scandinav 193 LXXVII 455
81 WECHSLER I S and BENDER M B Neurological manifestations of periarteritis nodosa Jour Mt Sinai Hosp 1942 VIII 1071
82 KING E F Ocular *involvement in a case of periarteritis nodosa* Transact Ophthal Soc United Kingdom 1935 LV 46
83 BOYD L V Periarteritis nodosa abdominal manifestations Bull N Y *Med Coll and Flower and Fifth Ave Hosps 1941 IV 7*
84 ELKELES A and GLYNN L E Serial rontgenograms of the chest in periarteritis nodosa as an aid to diagnosis Brit. Jour Radiol *1944 XVII 368*
85 LEVITT M F and BADER M E Effect of cortisone and ACTH on fluid and electrolyte distribution in man Am J Med 1951 XI 795
86 LUKENS F D W Medical Use of Cortisone including Hydrocortisone and Corticotropin Blakiston Co 1954 314 20 (chapter 5 by BAEHR G and LEVITT M F)

CHAPTER I-D

RETICULUM CELL SARCOMA

By HENRY JACKSON Jr and FREDERIC PARKER Jr

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RETICULUM CELL SARCOMA EXCLUSIVE OF THAT OF BONE

Part II

PRIMARY RETICULUM CELL SARCOMA OF BONE

PART I

RETICULUM CELL SARCOMA EXCLUSIVE OF THOSE OF BONE

TERMINOLOGY AND DEFINITION

This tumor is known by a confusing number of synonyms such as " Retothel sarcom large round cell sarcoma lymphosarcoma reticulum cell type and reticulocytoma As far as we can learn Ewing in 1913[1] first suggested that certain tumors might be derived from reticulum cells Many writers have given Roulet the credit of describing this type of tumor but Ewing definitely has priority since Roulet did not publish his paper until 1930

Many authors still regard reticulum cell sarcoma as one variety of lymphosarcoma and use the term lymphosarcoma reticulum cell type However we believe that reticulum cell sarcoma is a distinct entity from the point of view of histogenesis cell type pathological and clinical characteristics Some of the more important points of difference between the two types of neoplasms may be mentioned here A number of cases of lymphosarcoma are accompanied by a blood picture of lymphatic leukemia This is never seen in reticulum cell sarcoma Reticulum cell sarcoma of bone forms one group of primary bone tumors[3] In our experience on the other hand true lymphosarcoma never is primary in bone The age incidence of lymphosarcoma shows two main peaks one in the first the other in the sixth decade Generalized reticulum cell sarcoma arising in lymph nodes, on the contrary occurs chiefly in the fifth sixth and seventh decades and we have never seen a case under the age of 20 with the exception of those in which the disease was primary in bone The type cell of a lymphosarcoma is a lymphocyte that of reticulum cell sarcoma a reticulum cell each cell morphologically and physiologically entirely distinct and in the great majority of instances if the tissue is properly fixed and stained readily distinguishable from one another

The term reticulum cell in our opinion is unfortuante However the name has become so firmly entrenched that the substitution of any other would be unwise The term is unfortunate for several reasons Reticulum is used in two senses one to designate the fibrous supporting tissue of lymphoid tissue the other to define certain cellular constituents of these same tissues Therefore the term reticulum per se may mean either one of two separate types of structures and properly speaking the adjective fibrous or cellular should be added to define its exact meaning However in common usage the word reticulum alone is em

ployed to designate the fibrous supporting tissue and we shall use it in this sense A further objection to the expression reticulum cell is the fact that this cell does not produce reticulum but is merely associated with it as are many other cell types such as lymphocytes endothelial cells and the various parenchymatous cells of such organs as the liver and the kidneys

The Reticulum Cell

The reticulum cell according to our point of view is identical with the histio cyte clasmatocyte macrophage or large wandering mononuclear cell It is de rived from mesenchyma and appears in the embryo at about the same time as the fibroblast It occurs not only in lymphoid tissue but in varying numbers in all tissues In the central nervous system it bears the name of microglia In lymphoid tissue reticulum cells occur in the germinal centers or lie in the interstices of the reticulum fibers and often are applied closely to them

Due to various infections such as diphtheria and poliomyelitis the reticulum cells in the germinal centers of lymph nodes show evidence of marked phagocytosis the cytoplasm being filled with nuclear debris This cell also forms the cellular response to tuberculosis typhoid and syphilis in other words those dis eases to which the term granuloma commonly is applied Furthermore the giant cells found in the presence of a foreign body are derived from the reticulum cell The reticulum cell then responds to certain bacterial toxins and is also the chief scavenger cell of the tissues phagocyting necrotic cells of all types and attacking foreign bodies of any nature The littoral cells lining the sinuses of the lymph nodes may become free In such instances the cells are morphologically *and physiologically indistinguishable from reticulum cells This is also true of* the elements of the so-called reticulo-endothelium of other organs and tissues

In summary we believe that the reticulum cell is as much an entity as the fibroblast the smooth muscle cell or the lymphocyte It is not however derived from lymphocytes nor does it develop into them as some authors believe Tumors therefore arising from this cell should be termed reticulum cell sarcomas and they constitute a distinct type in no way related to neoplasms arising from cells of the lymphocytic series namely the true lymphosarcomas

From the considerations given above it is apparent that reticulum cell sar comas may arise from any organ or tissue in the body

The reticulum cell is considerably larger than a lymphocyte In tissue fixed in Zenker s fluid the nucleus which is from 1½ to 3 times larger than that of a lymphocyte varies in shape from round to oval frequently it is indented or lobu lated (Fig 1) In the cells of well differentiated tumors the chromatin is finely divided and scattered in the more anaplastic it tends to be coarse and nucleoli

may be prominent The cytoplasm is considerable in amount in relation to the nucleus and varies in its staining reaction from acidophilic to basophilic Evidence of amoeboid activity as indicated by the shape of the cell and its nucleus is present frequently Such amoeboid activity is not seen in the lymphocyte or lymphoblast Binucleate forms occur but true tumor giant cells do not The stroma varies in amount from delicate strands of collagen to dense bundles

By appropriate silver stains it may be seen readily that reticulum fibrils not only surround groups of cells but pass in an irregular manner between individual cells with which they are often in intimate contact

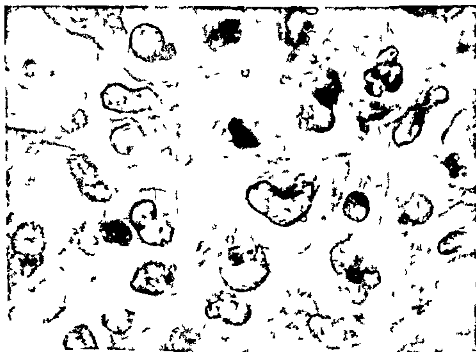


Fig 1 — Reticulum cell sarcoma Characteristic oval indented or lobulated nuclei

This histological picture the large irregular distorted nuclei, the scattered chromatin, the abundant and often amoeboid cytoplasm is hardly that of true lymphosarcoma in which the cells are uniform smaller and of more regular shape and in which the basophilic cytoplasm is scant and the chromatin gathered in heavy clumps

Point of Origin and Organ Involvement

From our 24 autopsies on cases of reticulum cell sarcoma, which occurred among a total of 17,459 autopsies at the Boston City Hospital it would seem that

the point of origin of the tumor was most common in the retroperitoneal nodes or in the gastrointestinal tract Occasionally it arose in the mediastinal or cervical nodes or in the pharynx Two tumors were primary in the substance of the brain (Table I)

TABLE I

RETICULUM CELL SARCOMA
APPARENT SITE OF ORIGI
24 AUTOPSIES*

		Number of Cases
Retroperitoneal nodes		8
Gastrointestinal tract		6
Stomach	4	
Colon	1	
Jejunum	1	
Mediastinal nod s		3
Cervical nodes		2
Temporal lob		2
Ton il		1
Sp l en		1
Il ac nodes		1

* E clu ive of tho e primary in bone con idered later

Clinical evidence sub tantiates the frequency with which the tumor originated in the gastrointestinal tract especially the stomach but indicates on the other hand a frequent origin in the pharynx especially the tonsil and in the cervical lymph nodes

The *lymph nodes* were involved by tumor in 22 of our 24 autopsied cases In 1 case the lymph nodes unfortunately were not examined as the pre ence of tumor was not recognized at the time of autopsy In 14 instances the tumor was primary in lymph nodes distributed as follows retroperitoneal 8 cases mediastinal 3 cases cervical 2 ca es and iliac 1 case The peripheral lymph nodes were found at autopsy to be involved in 10 instances the cervical nodes in 4 the inguinal nodes in 2 those of the axilla in 2 cases and both the cervical and inguinal nodes in 2 cases

The *gastrointestinal tract* was involved eventually in 12 of the 24 cases In 4 the condition was clearly primary in the stomach In each case the process was extensive in 1 virtually the entire stomach was involved In another the upper part of the lesser curvature most of the posterior wall and part of the greater curvature were implicated In the other 2 al o the lesion was extensive 1 being situated near the pylorus and the other along the greater curvature The descending colon was primarily involved in 1 ca e and secondary nodules varying in size

from pinhead to 1 to 2 cm almost invariably white in color, were found in various parts of the gastrointestinal tract In 2 cases such nodules were found in the stomach in 2 the rectum was implicated, and in similar fashion there were nodules in the esophagus and small intestine in 2 cases It is noteworthy that in but 1 case were the lesions ulcerated The clinical implications of this observation are obvious

The *liver* was involved in 10 cases in 2 there was both direct extension from a tumor primary in the stomach and metastatic nodules In the 8 other cases the lesions were purely metastatic Both the number and size of the metastatic nodules varied greatly Some were but a few millimeters in diameter, while others measured up to 3 centimeters in diameter Their shape was either spherical or irregularly linear when they followed the distribution of the portal areas The color of the nodules was white The size of the involved livers usually varied from normal to moderately enlarged In only 1 instance was the organ markedly enlarged weighing 3 790 grams

The *pancreas* was involved in 9 cases In 7 there were small metastatic nodules in 2 the organ had been surrounded and invaded by tumor of the retroperitoneal lymph nodes

The *spleen* was involved in 8 cases In 1 the tumor apparently was primary in that organ which weighed 1,300 grams The spleen was grossly involved in 7 cases and microscopically only in 1 The affected spleens were markedly increased in size the smallest weighing 660 grams and the largest 1,350 grams The tumor appeared as numerous greyish white nodules or bands of tissue varying in diameter from 1 millimeter up to several centimeters standing out against the normal red color of the pulp The capsule was not involved, although tumor nodules could be seen through it

In 7 cases tumor tissue was found in the *adrenals* most frequently as small nodules in the medulla Rarely the cortex was invaded

Primary reticulum cell sarcoma of *bone* is considered separately In our 24 cases of generalized reticulum cell sarcoma bone was involved in 7 cases In 1 there was direct extension to the hard palate in another the tumor had extended directly from the retroperitoneal lymph nodes to the lumbar vertebrae In 5 others small metastatic lesions were found chiefly in the vertebrae and the sternum

The *lungs* were affected in 6 cases In 3 the tumors were metastatic, and in 3 there was direct extension from other involved structures In 2 of the metastatic cases no gross tumor was visible In the third both lungs contained numerous firm grey red nodules varying in diameter from 2 to 3 cm In the 3 cases involved by extension 1 showed no gross tumor In 1 the tumor primary in the mediastinal nodes, extended into the right lung at the hilus distal to which the bronchi were dilated and filled with purulent material The left lung was not involved In

the third case the tumor was primary in the stomach and had extended upward through the diaphragm

Small metastatic nodules were found in the *kidneys* in 5 cases in the sixth case the organ was invaded from without and also studded with small metastatic nodules

The *heart* was invaded in 5 of our autopsied cases In 2 there was extensive involvement of the pericardium with bloody effusion in 2 there were isolated white nodules either in the auricle or pericardium In the fifth the heart weighed 380 grams and the tumor surrounded the pulmonary veins and arteries and the superior vena cava The neoplasm averaged 5 mm in thickness and numerous small polypoid growths were seen on the wall of the right auricle and along the course of the left descending coronary

The temporal lobe of the *brain* was the primary site of the disea e in 2 of our 24 cases These have been discussed in detail by Kinney and Adams In the third there was extension from the bone of the skull into the substance of the brain

In 1 case the tumor originated in the tonsil

As has been said reticulum cell sarcoma may arise in any part of the body Those tumors primary in the brain are of especial interest because of the great rarity with which this organ is implicated by any form of lymphoma[5] Those arising in the gastrointestinal tract are of importance because of their extent and their similarity to carcinoma Those arising in bone are of e pecial interest be cause though often extensive they are more amenable to appropriate treatment than most malignant tumors of bone

Incidence

In general reticulum cell sarcoma is a disease of elderly people though it is found occasionally in the twenties (Table II) and as will be di cussed later that form which is primary in bone is not uncommon in youth We cannot agree with Sugarbaker and Craver[6] that in lymphosarcoma reticulum cell sarcoma type the age distribution is very uniform nor do their own figures seem to support this contention

Sixty four of our 114 cases were men

Symptomatology

The common *initial symptoms* (Table III) reflect the invasive and destruc tive character of the condition Pain often constant and occasionally extreme is common and is liable to be resistant to the usual forms of irradiation therapy It is most common in the neck or deep in the abdomen It cannot we believe be

too strongly emphasized that persistently enlarged nodes in an adult in absence of obvious adjacent infection must be regarded as "neoplastic" until proved by

TABLE II

RETICULUM CELL SARCOMA*
AGE AT ONSET
114 CASES

Age	Number of Cases
0–9	0
10–19	0
20–29	11
30–39	6
40–49	25
50–59	9
60–69	28
70–79	13
80–89	2

* Exclusive of primary reticulum cell sarcoma of bone

TABLE III

RETICULUM CELL SARCOMA
INITIAL SYMPTOMS
114 CASES

	Number of Cases	
Pain		41
Head and neck	14	
Abdomen	13	
Chest	7	
Leg	7	
Enlarged lymph nodes		24
Cervical	21	
Inguinal	3	
Sore throat		23
Dysphagia		10
Loss of weight		10
Vomiting		7
Nasal obstruction		6
Dyspnea		5
Epistaxis		4
Enlarged tonsil		4
Weakness		4
Hoarseness		3
Edema, cough, melena, deafness, skin nodules		1 each

biopsy to be of benign or infectious nature. Enlarged lymph nodes usually in the cervical region are frequent early in the course of the disease though superficial painless lymphadenopathy as the only initial symptom is far less common than in Hodgkin's granuloma or Hodgkin's paragranuloma. The nodes not infrequently are painful, occasionally tender and usually firm or even of the stony hard consistence usually regarded as characteristic of metastatic carcinoma. In sharp contrast to Hodgkin's granuloma the nodes not infrequently are fixed to the underlying tissues and occasionally the overlying skin is thickened and of a dull brownish red color. The firm consistence of the nodes and their tendency to fixation is of some value in the clinical differentiation of reticulum cell sarcoma from Hodgkin's disease. Long continued sore throat was an initial symptom in over 20 per cent of our cases and the persistence of this symptom for any great length of time in an elderly patient always should arouse the suspicion of malignant disease particularly if associated with bleeding, notable enlargement of the tonsil or other symptoms suggestive of neoplastic disease. Dysphagia was found to be an occasional initial complaint. It may be caused by pressure from enlarged lymph nodes or much more rarely by an intrinsic lesion of the esophagus itself. Loss of weight is frequent even early in the disease. Nasal obstruction often intermittent and associated with a purulent or more rarely a sanguinous discharge is an uncommon but important initial symptom as pharyngeal reticulum cell sarcoma is one of the most formidable and distressing forms of the disease. These nasal symptoms in elderly people when not caused by obvious infection must be evaluated very carefully. The remaining initial symptoms which have been encountered in our series further attest the malignant and destructive character of the disease.

Chills, fever, general malaise and sweating are conspicuously absent, particularly so in contrast to Hodgkin's granuloma.

It has been pointed out already that reticulum cell sarcoma may arise in any organ of the body and of course any organ may be invaded subsequently either directly or by metastatic nodules (Table IV). This is true also in Hodgkin's disease but from a clinical point of view there is a very great difference between these conditions not only in regard to their initial symptomatology but also in respect to the organ involved. In reticulum cell sarcoma neither the mediastinum nor the lungs are involved nearly so commonly as in Hodgkin's granuloma or sarcoma, nor are the liver and spleen, and these latter organs even when involved are not apt to reach the massive size often seen in Hodgkin's disease. On the other hand clinical evidence of secondary bone lesions is relatively uncommon in reticulum cell sarcoma (16 per cent) as compared to Hodgkin's sarcoma (50 per cent) though rarely one sees massive bone destruction apparently secondary to a focus elsewhere and similar to the massive primary reticulum cell sarcoma of bone to

be described later Involvement of the pharynx is common in reticulum cell sarcoma (34 per cent) rare in Hodgkin's sarcoma (15 per cent) and exceedingly rare in Hodgkin s granuloma Of the pharyngeal tumors, those of the tonsils are by far the most frequent

TABLE IV

RETICULUM CELL SARCOMA
ORGANS INVOLVED CLINICALLY IN 98 CASES
FOLLOWED TO DATE OR TO DEATH

		Number of Cases
Superficial lymph nodes		71
Pharynx		31
Tonsil	23	
Nasopharynx	8	
Palate	5	
Posterior pharynx	3	
Multiple	6	
Gastrointestinal tract		19
Stomach	10	
Esophagus	3	
Ileum	3	
Cecum	3	
Rectum	3	
Sigmoid	1	
Multiple	1	
Mediastinal nodes		15
Spleen		15
Bone (secondarily involved)		15
Skin		13
Liver		10
Nervous system		10
Lungs		7
Breast		4
Genitourinary tract		2
Thyroid		1

Clinical evidence of the *involvement of the gastrointestinal* tract is seen in approximately 20 per cent of the cases The lesion usually is single and is most common in the stomach where it may give rise to symptoms indistinguishable from those of carcinoma namely epigastric pain anorexia vomiting hematemesis and often marked and rapid loss of weight Unfortunately such lesions often are silent

Gross lesions elsewhere in the gastrointestinal tract *similarly* give rise to pain and occasionally are associated with a palpable mass Rarely there may be

an isolated solitary tumor amenable to surgical removal with some hope of permanent cure. Perforation occurs rarely, but the tumor has a strong tendency to infiltrate neighboring organs and extend to local lymph nodes. Involvement of the brain has been referred to already. The implication of peripheral or cranial nerves is not uncommon, giving rise to palsies of various sorts, often amenable to appropriate radiation.

Blood. — A slight degree of normochromic or hypochromic anemia is seen in approximately 35 per cent of the cases. Severe anemia is very rare. In only 6 of our cases did the red count fall below 3,000,000, and in but 2 was a level less than 2,000,000 reached. In each of these latter cases the disease was unusually widespread, and in each anorexia and loss of weight were extreme. The comparative absence of marked anemia in this disease is noteworthy when contrasted with Hodgkin's granuloma.

The white count does not deviate greatly from the normal. Very rarely there is a moderate (15,000 to 20,000) leukocytosis. Leukopenia we have never encountered. In some cases there is a moderate and in a rare case a marked increase in the percent of polymorphonuclears. Again the sharp contrast between this disease and Hodgkin's granuloma is striking.

As has been stated already, we have never seen the development of lymphatic leukemia referred to by Sugarbaker and Craver[8] as a "not infrequent termination of reticulum cell lymphosarcoma." Very rarely histiocytic leukemia does develop. Certainly it is true that there is no characteristic blood picture of reticulum cell sarcoma.

Symptoms Developing in Course of Disease. — Once the condition has made itself manifest further symptoms are not slow in appearing and these once more indicate the destructive nature of the disease (Table V). It is to be noted in particular that loss of weight and pain are common and often extreme. We have seen 1 patient die apparently from excessive, continual and irremediable pain. Sore throat, dysphagia, hemoptysis, hematuria, melena and nasal obstruction are seen more commonly during the course of the disease than in any other form of lymphoma*.

On the other hand pronounced fever unless due to associated sepsis is rare, and the itching and marked tachycardia so common even early in Hodgkin's granuloma is almost never encountered. The so-called Pel-Ebstein fever does not occur in this condition.

The usual course of the disease is relentlessly onward. The spontaneous remissions occasionally seen in Hodgkin's granuloma do not, in our experience, occur.

* This word is used for lack of a better one to cover Hodgkin's disease, reticulum cell sarcoma, lymphosarcoma and giant follicle lymphoma.

Diagnosis

It is doubtful whether a clinical diagnosis of reticulum cell sarcoma can be made with any degree of certainty As with other forms of malignant lymphoma a biopsy is necessary and it is imperative that the tissue be well fixed preferably in Zenker s fluid and well stained It is our opinion, and it was that of Ewing

TABLE X

Reticulum Cell Sarcoma
Symptoms Developing during Course
98 Cases

	Number of Cases
Loss of weight	64
Pain	54
Anorexia	36
Dyspnea	1
Cough	15
Edema	14
Sore throat	14
Fever	13
Vomiting	1
Melena	10
Dysphagia	8
Effusion	7
Nausea	7
Nasal obstruction	7
Diarrhea	6
Hemoptysis	6
Jaundice	6
Hoarseness	6
Hematuria	5
Enophthalmos	5
Hematemesis	5
Ascites	3
Constipation	3
Chills	2

that improperly fixed thick poorly stained sections are the cause of much of the confusion arising in this already complicated field of lymphoma

When superficial lymph nodes are the sole objective evidence of the disease reticulum cell sarcoma may be indistinguishable from Hodgkin s granuloma Hodgkin s sarcoma carcinoma tuberculosis or even sarcoid The disease may be suspected however, when the involved lymph nodes are hard somewhat fixed to

the underlying or overlying tissues and painful As has been said the overlying skin occasionally is reddened and thickened The absence of fever the presence of a normal white cell count and differential cell count are of some importance in the differential diagnosis

When the mediastinal nodes are involved primarily an exact diagnosis can be made only by biopsy of a superficial metastatic node In the presence of such symptoms as loss of weight anorexia and dyspnea it is patent that a careful physical and x ray examination is in order and it is important to recall that the process may be entirely internal and that therefore the diagnosis may be difficult or indeed for a time impossible

In the pharynx the disease may be suspected in the presence of a bulky obstructive tumor that is often painful in a comparatively young person 25 to 50 years old A similar tumor in an older person cannot be differentiated clinically from carcinoma

Similar principles can be applied with some measure of success to reticulum cell sarcoma of the gastrointestinal tract though it should be remembered that carcinoma of the stomach is not rare in comparatively young persons

Illustrative Cases

The following cases illustrate some of the more important types of the disease

Case 1 M C B C H #756097 This 44 year old man was admitted to the hospital on March 14 1935 In January 1934 he began to have severe intermittent frontal headaches particularly on the right side Six months later he became increasingly deaf in the right ear and at the same time he noticed enlarged hard non tender lymph nodes high in the right neck One of these was removed and showed the typical picture of reticulum cell sarcoma (S34–2666) During the succeeding 2 months 2 000 r of x ray were given to the right side of the neck with much relief of symptoms In September 1934 the patient complained of nasal obstruction and on physical examination there was found a large polypoid tumor which nearly filled the nasopharynx Biopsy of this mass again showed reticulum cell sarcoma The headaches and deafness recurred and increased in severity and enlarged nodes were noted for the first time in the left side of the neck in both anterior and posterior triangles During the next 2 months he received a total of 3 400 r of x ray divided equally between the two sides of the neck He left the hospital against advice and at another institution received an additional 4 000 r Following this treatment all the enlarged lymph nodes disappeared but the patient returned to our clinic and was admitted to the medical ward Physical examination in March 1935 showed a few small very hard fixed lymph nodes in either side of the neck There was no other lymphad

enopathy The nasopharyngeal tumor was still present though much smaller The patient was completely blind in the left eye There was marked ptosis of the left lid and paralysis of the left abducens nerve X ray films showed some destruction of the inferior orbital plate on the left side The remainder of the physical examination was essentially normal The patient complained of severe, constant, left sided headache Further high voltage x ray therapy brought no relief Six weeks after this hospital admission there developed a complete left facial paralysis The headache became increasingly severe The patient rapidly lost weight and died on June 17 1935 18 months after his first symptom Throughout his illness the red blood cell count had remained essentially normal At no time was there an elevated white blood cell count, though there was a constant, marked increase in the percent of polymorphonuclears No fever was present at any time The basal metabolic rate at all times was normal

Both deafness and various ocular disturbances such as blindness and enophthalmos are not unusual in reticulum cell sarcoma The eye signs, especially enophthalmos may respond quite dramatically to appropriate x ray therapy

Case 2 E D P #7192 This 23 year old man first noted nasal obstruction and bilateral painless enlargement of the cervical lymph nodes in January, 1930 In October 1930 he was admitted to another hospital for increasing nasal obstruction and a unilateral purulent, nasal discharge At that time a tonsillectomy was performed and a diagnosis of lymphoblastoma ' was made An unknown amount of irradiation was applied to the neck The symptoms subsided, and the patient remained in fairly good health until March 1932, when he was admitted to the Collis P Huntington Memorial Hospital complaining once more of marked nasal obstruction and severe pain in the left ear On entry physical examination revealed no abnormalities except for a large polypoid mass nearly filling the nasopharynx A biopsy of this tumor showed it to be reticulum cell sarcoma His red blood cell count was 3 920 000, hemoglobin 80 per cent The white blood cell count was 9 300 the differential normal During the next 2 months 4,200 r of x ray were directed to the tumor but there was no favorable response The patient complained of increasing anorexia deafness and earache He lost 30 pounds of weight The patient gradually failed the earache became extreme and could be controlled only by large doses of morphine Death occurred from bronchopneumonia early in January 1934 4 years from onset

Autopsy (PA34-16) showed marked cachexia and bilateral bronchopneumonia The reticulum cell sarcoma was confined to the nasopharynx the left tonsillar fossa and the cervical lymph nodes

Case 3 F J S D #76642 This 48 year old man was sent in to the hospital with a diagnosis of diphtheria For 10 days prior to admission he had suffered from an increasingly severe sore throat For 4 days he had had pain in the right

ear The past history was irrevelant On entry physical examination was essentially negative except that a yellowish grey membrane covered the uvula and the right side of the soft and hard palate portions of which were deeply ulcerated The peripheral blood picture was essentially normal The Wassermann reaction was positive While in the hospital he ran a moderate degree of fever A tentative diagnosis of syphilis was made and the patient was treated with sulpharsphenamine and potassium iodide Despite these therapeutic measures however, the ulcerations continued to spread and during the ninth hospital week the major part of the palate sloughed away leaving a large perforation into the nasal cavity During the twelfth hospital week the patient s pulse rose to 130 and the respiration to 35 He frequently spat up large amounts of very foul sanguinopurulent material The patient grew progressively weaker and the red blood cell count dropped to 2 500 000 The white blood cell count and differential remained essentially normal He died on May 4 1927

Autopsy (A27–168) showed very extensive reticulum cell sarcoma of the hard and soft palate the tonsils and posterior pharyngeal wall with extension to the maxilla nasal septum base of the tongue and larynx There were in addition metastases to the lungs liver spleen and heart and accumulations of sterile pus in the peritoneal and pericardial cavities

Each of these cases illustrates the invasive destructive and often comparatively localized nature of the condition as well as the relatively poor response to irradiation

A more unusual type of this disease is illustrated by the following case

J D #840386 This 50 year old Italian was admitted to the hospital on November 3 1936 His past history was irrevelant For a period of 2 weeks prior to admission he had complained of increasing drowsiness and severe headaches On several occasions he had vomited Physical examination showed an exceedingly drowsy weak somewhat disoriented man The pupils were normal The tongue deviated to the left There was marked weakness of the left arm and leg and all tendon reflexes on the left side were increased There was a positive Babinski reaction on the left Otherwise the physical examination showed no noteworthy abnormalities A lumbar puncture showed an initial pressure of 240 mm and a pressure of 140 mm after the withdrawal of 10 cc of clear pale amber fluid The spinal fluid showed 7 lymphocytes and 9 red cells per cu mm The Pandy test for globulin was 24 The total protein of the spinal fluid was 120 mgm per 100 cu mm The Wassermann reaction was negative The gold curve was 0112222110 The patient remained in the hospital for 12 days gradually growing weaker The neurological signs remained essentially the same Bronchopneumonia developed at the right base and on the twelfth hospital day he sank into a deep coma and died 8 hours later

Autopsy (A36–395) showed an extreme degree of cerebral edema and a moderately large tumor mass in the central portion of the right hemisphere with invasion of the claustrum external capsule and lateral edge of the right internal capsule (5)

That the outlook for patients with reticulum cell sarcoma is not always so gloomy as would appear from those just cited is attested by the following histories

Case 4 M N HH #36–113 This 54 year old Armenian man was seen first in February 1936 A month before he had noted enlarged nodes in each neck and axilla His past history was irrelevant and there had been no loss of weight Physical examination showed several, olive sized, hard, non tender, lymph nodes in each axilla and in either side of the neck under the sternomastoid muscle Otherwise the physical examination was essentially normal The peripheral blood showed a slight degree of secondary anemia otherwise no abnormalities A biopsy of a cervical node (HS36–349) showed the typical histological picture of reticulum cell sarcoma He was given 1 200 r of x ray to each side of the neck and 1 400 r to each axilla Two months later all enlarged lymph nodes had disappeared and the patient felt entirely well He remained symptom free until April 1937 when he complained of epigastric distress and some difficulty in swallowing solid food X ray films showed a definite filling defect in the lower third of the esophagus He was given 600 r of x ray to the involved area and the symptoms entirely disappeared One month later another film showed no esophageal lesion Except for minor episodes of lymphadenopathy, which responded well to irradiation the patient was well when last seen (December 1942), 7 years from onset

Case 5 G A P #9322 This 23 year old man was seen first in May, 1935 In November 1934 he developed severe constant pain in the right lower quadrant There was no vomiting diarrhea constipation or melena He was examined in an outside hospital at that time and a mass was felt in the region of the appendix A transverse ileocolostomy was performed On admission in May, 1935 physical examination revealed a very tender orange sized mass in the right lower quadrant Otherwise the physical examination was normal There was no loss of weight and the peripheral blood picture was normal The abdomen was opened and a mass was found involving the cecum and adjacent mesenteric lymph nodes A right colectomy was performed All involved tissue was removed and postoperatively 1 200 r of x ray was given to the anterior and 1, 00 r to the posterior abdomen Convalescence was uneventful and the patient is alive and well to date (May 1944) 9 years after operation

This single case sent to the hospital with a diagnosis of inoperable carcinoma of the intestine, attests the value of courageous radical surgery in a small number of cases

Treatment

The treatment of choice in those forms of reticulum cell sarcoma which are not amenable to surgical intervention (and it must be confessed that very few are) is heavy irradiation with high voltage x ray though it must be said that this form of therapy is not always attended by any notable degree of success Often however, the results of x ray are at least temporarily gratifying as in the case of L T (I #1301) whose cervical nodes though very extensive disappeared completely in a short time and did not reappear Two years later the patient noted increasing constipation and a barium enema showed an obstructing tumor at the rectosigmoid junction He refused all treatment however and died 6 months later It is not improbable that irradiation of the gastrointestinal lesion would have prolonged his life still further For those cases in which the disease appears to be more or less generalized our experience would lead us to believe that heavy doses of x ray are indicated We are inclined to favor the x ray therapy program outlined by Sugarbaker and Craver' and to advocate as they do a total dosage of 2 000 r to 3 000 r to each area involved this amount to be given over an appropriate period of time If the process is sharply limited yet not amenable to radical intervention as for example in the nasopharynx we would advocate such dosages of x ray as are employed in carcinoma namely from 5 000 to 8 000 r over an appropriate period of time Further x ray therapy should be withheld until new signs or symptoms require treatment It is our firm belief that the roentgenologist and clinician should follow the patient together and that decisions as to treatment should be reached in consultation It is hardly necessary to point out that the treatment of each case must be individualized If the process is apparently sharply confined and no distant metastases are apparent radical surgery seems clearly to be indicated It should be remembered however that like other sarcomas the pathological process not infrequently extends beyond the limits that are obviously diseased and therefore, excision should be wide

Prognosis

In general the prognosis of reticulum cell sarcoma is poor (Table VI)

Neither age nor sex appear to be of any particular prognostic import In general those patients whose initial symptom is merely painless lymphadenopathy have a relatively good prognosis Of the 22 cases in whom the disease first manifested itself in this manner 55 per cent survived the 3 year period and the average duration of life in this group was 3 6 years 5 survived over 6 years On the other hand when the disease begins with pain or with symptoms such as dyspnea melena or hematemesis indicating involvement of internal organs the

outlook is correspondingly poor Seventy five per cent of the patients, who lived more than 3 years had painless enlargement of superficial lymph nodes as the first obvious sign of the condition while of those patients who lived 6 months or less nearly 90 per cent had initially either pain or some symptom indicating

TABLE VI

RETICULUM CELL SARCOMA

DURATION FROM ONSET TO DEATH 88 CASES

Years	Number of Cases	Per Cent
0.0–1.0	46	52
1.1–3.0	36	41
3.1–10.0	5	6
Over 10	1	1
DURATION FROM ONSET TO DATE 10 CASES		
0.0–1.0	2	20
1.1–3.0	5	50
3.1–10.0	2	20
Over 10	1	10

DIED OF UNRELATED CAUSES

3

LOST

13

visceral involvement Neither splenomegaly nor hepatomegaly appear to be of prognostic importance but involvement of the mediastinal nodes the lung or the gastrointestinal tract is of ill omen Fourteen of our 18 cases that lived less than 6 months from onset had involvement of either the lung mediastinal lymph nodes or gastrointestinal tract and all of those patients with mediastinal or gastrointestinal tract involvement died within less than 1 year of onset except 1, in whom the disease was discovered comparatively early so that radical surgical intervention could be carried out with *apparent success* *It should be remembered* that as in other forms of malignant lymphoma sudden death may occur

BIBLIOGRAPHY

1 EWING J Endothelioma of lymph nodes Jour Med Research 1913–14 XXVIII 1

2 ROULET F Das primare Retothelsarcom der Lymphknoten Virchows Arch f path Anat 1930 CCLXXVII 15

3 PARKER F JR and JACKSON H JR Primary reticulum cell sarcoma of bone Surg Gyn and Obst 1939 LXVIII 45

4 KINNEY T D and ADAMS R D Reticulum cell sarcoma of the brain Arch Neurology and Psychiatry 1943 L 55
5 YUILE C L Case of primary reticulum cell sarcoma of the brain Arch Path 1938 XXVI 1036
6 SUGARBAKER E D and CRAVER L F Lymphosarcoma a tudy of 196 cases with biopsy Jour Am Med Assoc 1940 CXV 1,

October 1 1944

Part II

PRIMARY RETICULUM CELL SARCOMA OF BONE

Incidence and Pathology

In 1939 reticulum cell sarcoma of bone was added to the list of primary bone tumors in the revised classification of the Registry of Bone Sarcoma of the American College of Surgeons.[1] Thirteen of these neoplasms previously had been classified as Ewing's sarcoma, Hodgkin's disease, lymphosarcoma, osteogenic sarcoma or as an inflammatory process. In view of the fact that primary reticulum cell sarcoma of bone has been readily diagnosed only recently and because the prognosis is comparatively good if the disease is promptly and radically treated, it seems appropriate to devote a special section to its consideration. The clinical and pathological aspects of this tumor were reported in some detail by us in 1939.

From the Registry of Bone Sarcoma we have collected 13 cases and from our own material we have added 12 more. Of the 25 cases 13 were men and 12 were women.

The age distribution of primary reticulum cell sarcoma of bone differs materially from that of the generalized or soft tissue form of the disease which, as has been pointed out already, is primarily found in middle and old age, 85 per cent of the cases occurring after the age of 40 and none of our series being under 20 years of age. In sharp contrast, as will be noted in Table I, 64 per cent of the primary reticulum cell sarcomas of bone occurred under the age of 40 and 28 per cent below the age of 20. In view of the highly malignant nature of most primary bone tumors in the early decades these facts should be clearly recognized.

TABLE I

Primary Reticulum Cell Sarcoma of Bone
Age at Onset
25 Cases

Age	Number of Cases
0– 9	0
10–19	7
20–29	3
30–39	6
40–49	3
50–59	3
60–69	3

In the generalized form of the disease the rather uncommon metastatic bone lesions occur most often in the vertebrae and skull On the contrary primary reticulum cell sarcoma of bone is found most frequently in the long or flat bones (Table II)

TABLE II

PRIMARY RETICULUM CELL SARCOMA OF BONE
BONE INVOLVED
25 CASES

Bone	Number of Cases
Femur	5
Clavicle	5
Tibia	5
Humerus	4
Vertebra	3
Scapula	1
Mandible	1
Maxilla	1

The type cell is identical with that of reticulum sarcoma of lymph nodes and other tissues

A fairly common feature of these tumors is the growth of cells in the walls of small veins In such vessels the endothelium is lifted and the lumen encroached upon and distorted by tumor cells in the intima We have not seen similar involvement of the arteries or arterioles Necrosis of the infarct type often is a prominent feature Complete destruction and obliteration of the normal constituents of the marrow is found constantly Osteolysis often is a prominent feature The tumor cells do not form new bone but new bone formation by stroma does occur

Metastases fortunately are late and are seen chiefly in the neighboring lymph nodes In only 1 instance (#1951) have we seen evidence of pulmonary metastase In another case a nodule appeared in the breast 2 years after an incomplete resection of an involved clavicle

In gross appearance the tumor varies considerably In early cases the medullary cavity is invaded by pinkish grey granular neoplastic tissue In more advanced cases there is more obvious bone destruction and the soft tissue involvement already referred to is obvious The tumor in these instances usually is firm smooth and glistening more rarely it is soft and friable The color is described variously as pale white pinkish grey and grey white Areas of necrosis are frequent and may merge into large cavities resembling osteomyelitis

Symptomatology

Clinically the onset is similar to that of many other primary bone tumors, namely with pain not relieved by rest Pain localized at the site of disease or referred to the point nearest the tumor was the first symptom in 20 cases in 3 a pathological fracture brought the patient to the physician, in 2 a painless swelling of the bone and surrounding soft parts was the chief initial complaint In 10 cases there was an obvious tender swelling of the affected part It is to be particularly noted that the general health of the patient when first seen, was good in all but 2 cases (#547, #1663) In these 2 there had been great loss of weight and strength yet both cases are alive and well over 10 years later In 3 cases the spine was involved One of these has been described in detail by Edwards[4] Another was operated upon and the tumor completely removed Unfortunately the patient died of respiratory failure shortly thereafter In no case was fever noted In no instance were there notable abnormalities in the peripheral blood picture The few blood calcium and phosphatase determinations which have been done were within normal limits but the number of determinations are too few to be of significance A history of injury preceded the initial symptoms in 6 of the 25 cases but there is no good evidence that trauma actually is of etiological importance It seems more probable that a minor injury brought on symptoms in already diseased bone or that a previous injury was recollected by the patient, when symptoms of major importance had supervened Perhaps the most important clinical feature is that an extensive painful destructive process most often in a long bone is found in a patient of any age whose general condition usually is good In no other bone sarcoma is the contrast between the comparative well being of the patient and the extent of the lesion so marked With no other bone tumor may the lesion be so extensive and at the same time be so amenable to appropriate treatment

Often the disease had existed so far as one could tell by the symptomatology, for many months before the services of a physician were sought In 7 cases symptoms had been present for a year or more before treatment yet 5 of these patients are alive and apparently well from 3 to 16 years later This very fact attests the comparatively benign nature of what appears roentgenographically clinically and histologically to be a highly malignant tumor The importance of the recognition of this fact in relation to therapeusis is obvious

Diagnosis

We ought however to emphasize the necessity of early diagnosis and treatment for by these means only can one expect to obtain the best results In 1

instance the signs and symptoms definitely pointing to a tumor of the femur had been present for a year and 4 months before amputation and the condition had been diagnosed variously as tuberculosis and arthritis At the time of operation the tumor had reached massive size and inguinal lymphadenopathy was present The patient died 3 months later It is not improbable that had an accurate diagnosis been made by biopsy at an earlier date the results would have been better In the presence of a malignant bone tumor it does not pay to temporize

The *x ray appearance* is by no means diagnostic The disease is seen most frequently in the ends of the long bones and extends from the metaphysis to the diaphysis In general x ray examination shows chiefly bone destruction and to a much less degree bone formation Occasionally pathological fracture is seen as it may be in the metastatic forms of reticulum cell sarcoma In early cases there may be only mottled bone destruction in the medulla In 1 early case very fine hair like striations extended from the irregularly thickened cortex and periosteum into the adjacent soft tissue giving rise to a picture not inconsistent with osteo genic sarcoma There is often fragmentation of the cortex and a widening of the shaft as if from an expansion tumor pressing from within outward Periosteal thickening may be seen both early and late in the disease as it may in the meta static lesions secondary to the generalized form of reticulum cell sarcoma Inva sion of the surrounding muscle is not uncommon In 1 case this invasion was so extensive that for some time the tumor was thought to have originated in the soft parts rather than the bone

Differential Diagnosis

Reticulum cell sarcoma of bone must be distinguished from the following con ditions with which it has been confused in the past

Hodgkin s Disease —The granulomatous form of this condition with sclerosis necrosis eosinophils and Reed Sternberg cells should present no diagnostic diffi culty The sarcomatous form in which the majority of the cells are of the mono-nuclear type may simulate closely anaplastic reticulum cell sarcoma but the presence of occasional typical Reed Sternberg cells should serve as a differential point Primary Hodgkin s disease of the bone we believe to be very rare

Lymphosarcoma —The type cell with its round nucleus scanty cytoplasm and spherical shape should offer no difficulty In our experience true lymphosar coma of the bone is extremely uncommon

Ewing s Sarcoma —Reticulum cell sarcomas most frequently have been diagnosed erroneously as Ewing s tumor In the latter the uniform appearance of the cells and of their nuclei their arrangement in strands and cords and the distribution of the reticulum are diagnostic features In Ewing s sarcoma the

reticulum surrounds groups of cells, while in reticulum cell sarcoma not only does the reticulum surround groups but also runs between individual cells

Osteogenic Sarcoma — Some of the reticulum cell sarcomas have been diagnosed as atypical osteogenic tumors The lack of any tumor bone or tumor cartilage formation, the absence of osteoid tissue and the morphology of the tumor cells should exclude this diagnosis

Inflammation — The diagnosis of inflammation in the past has been made erroneously on several reticulum cell sarcomas The presence of large mononuclear cells and lymphocytes with in addition necrosis has proved misleading In 1 of our own cases the infarct type of necrosis and the marked cellular infiltration of the vessel walls lead to an incorrect diagnosis of syphilis Even on a biopsy specimen this error may be made unless the examination is sufficiently complete and extensive to include visible tumor cells

Illustrative Cases

The following cases illustrate the course of the disease

W B #564 A single man aged 44 years was admitted to the Massachusetts General Hospital on October 1 19 4 His past history was uneventful

Since January 1924 he had had moderate pain in the right upper arm In May 1924 while playing baseball he fractured his right humerus An x ray film taken at this time showed no evidence of tumor The bone however did not unite well and in August 1924 the patient noticed a swelling of the middle of the right upper arm Although the pain decreased, the tumor increased in size An x ray examination on October 1924 showed destruction of the humerus throughout nearly its entire extent There was little if any new bone formation, although there had been a fracture in the midportion 6 months before this The new growth extended nearly to the head of the humerus The proximal portion of the ulna appeared to be involved by a similar process

On October 9 1924 a shoulder joint amputation was performed In 1924 this tumor was diagnosed as osteolytic sarcoma In 1925 a diagnosis of osteogenic sarcoma was made In 1934 it was first suggested that the tumor was a reticulum cell sarcoma the diagnosis being based on the criteria set forth in this paper

Convalescence was uneventful and the patient remained entirely well until October 1931 when a tumor developed in the amputation scar This mass was excised and showed the same histological picture as did the original bone tumor The patient has remained well and active to date, May 1944 19 years from the onset of symptoms

W S #1663 A 15 year old boy who aside from the usual childhood diseases

had been quite healthy In the spring of 1927 he noticed a tender swelling in the region of the left knee Radium in unknown doses was applied and the pain and swelling completely receded for a period of 6 months All symptoms then returned and the patient lost 30 pounds in weight An x ray examination on March 25 1929 showed an irregular lesion involving the cortex and medulla of the proximal third of the shaft of the tibia The lesion was mottled in appearance due to irregular zones of bone destruction intermingled with dense zones of new bone formation The cortex was roughened and the periosteum lost in a large soft tissue swelling enveloping the knee A diagnosis of Ewing s tumor was made and amputation was done March 26 1929 This specimen was diagno ed in 1934 as Ewing s sarcoma in 1936 as questionable reticulum cell sarcoma or as Ewing s tumor In 1936 a definite diagnosis of reticulum cell sarcoma was made Recovery was uneventful and the patient was well and free from symptoms or signs of disease 11 years after the onset of the tumor

H B #37–1599 A boy aged 14 years sustained a rather violent blow on the right jaw in July 1937 A month later he noted a lump on the right lower jaw There was no pain and the patient s general condition was good He was admitted to the hospital on December 31 1937 At that time there was found on the outer side of the right mandible a hard non tender tumor 3 x 3 x 2 cm There was no cervical or generalized lymphadenopathy The remainder of the physical examination was essentially normal The red blood cell count was 4 950 000 the hemoglobin 90 per cent the white blood cell count 8 100 and the differential normal The blood calcium was 10 8 the blood protein 4 3 and the phosphatase 0 35 units X ray films showed fine striations extending into the soft ti sues and some increased density below the roots of the first two molar teeth A biopsy of the tumor showed reticulum cell sarcoma The right mandible was resected and 1 500 r of x ray was given to the right side of the neck The patient with an artificial mandible was alive and well 6 years from onset

Treatment

It is impossible at present to conclude exactly what the best form of treatment is Amputation followed by irradiation to the adjacent lymph nodes however appears to give the best re ults In one instance excision seemed adequate but we believe that amputation should be done whenever possible In addition prophylactic radiation is advisable A biopsy of the lesion may be done safely prior to amputation but it should be emphasized that only by careful microscopical study of a properly fixed and stained section can the correct diagnosis be made

Five of the cases studied received radiation only The results as can be seen from Table III were not encouraging

TABLE III

PRIMARY RETICULUM CELL SARCOMA OF BONE
RESULTS OF RADIATION ONLY

Age	Sex	Result	Duration from Onset (months)	Remarks
35	M	Dead	22	Tumor unaffected
60	F	Dead	24	Tumor unaffected
58	F	Dead	48	Metastases
14	M	Alive	3	Tumor decreased in size
15	F	Alive	24	Tumor unchanged

Three additional cases had initial radiation with complete disappearance of both signs and symptoms of the tumor but in each instance the tumor recurred locally within 6 months Amputation was then done and all 3 patients are alive and apparently free from disease from 10 to 14 years from onset The e facts point at the same time to the comparative inefficiency of radiation alone and the value of amputation

TABLE IV

PRIMARY RETICULUM CELL SARCOMA OF BONE
RESULTS OF AMPUTATION OR EXCISION ONLY

Age	Sex	Result	Duration from Onset	Remarks
42	M	Dead	24 hours	Postoperative death
65	F	Dead	2 months	Excision of maxilla
63	F	Dead	4 months	Incomplete resection tumor of 8th dorsal vertebra
31	M	Dead	1 year 3 months	Mid thigh amputation
12	F	Dead	12 years	Cause death unknown
15	M	Alive	4 months	Clinically well
36	F	Alive	2 years	Clinically well
29	M	Alive	3½ years	Clinically well
24	F	Alive	6 years	Clinically well
56	F	Alive	7 years	Clinically well
58	F	Alive	12 years	Clinically well

Eleven cases had amputation or incision only There were 5 deaths One patient died somewhat over a year after a mid thigh amputation for an extensive lesion of the femur A hip joint amputation would have been preferable One patient died 12 years from onset of an unknown cause the case having been lost sight of One patient died shortly after an attempted removal of all diseased

TABIE V

PRIMARY RETICULUM CELL SARCOMA OF BONE
RESULTS OF AMPUTATION AND PROPHYLACTIC RADIATION

Age	Sex	Result	Duration from Onset	Remarks
48	F	Dead	2 years	Meta tases at operation
14	M	Alive	6 years	Clinically well
36	M	Alive	8 years	Clinically well
18	F	Alive	10 years	Clinically well
14	M	Alive	14 years	Clinically well
44	M	Alive	16 years	Clinically well

tissue invading the maxilla and antrum Two patients died shortly after the attempted removal of a comparatively localized tumor of the spine The remainder of the cases are alive and apparently well (Table IV)

In 6 cases amputation was followed by x ray therapy One patient so treated died with pulmonary and lymph node metasta es after the amputation of a massive tumor of the femur which had been present already for over a year and from which the inguinal lymph nodes had become involved before operation The remainder of the patients in this category are alive and well (Table V)

It should be emphasized again that primary reticulum cell sarcoma of bone is an easily recognizable entity occurring at any age presenting rather variable x ray features and not infrequently mistaken for other bone diseases both neoplastic and inflammatory If recognized early and attacked vigorously the prognosis eems good in spite of the apparent malignant nature of the tumor

BIBLIOGRAPHY

1 EWING J Review of classification of bone tumors Surg Gyn and Obst 1939 LXVIII 971
2 SIMMONS C C Bone sarcoma factors influencing progno is Surg Gyn and Obst 1939 LXVIII 6
3 PARKER F JR and JACKSON H JR Primary reticulum cell sarcoma of bone Surg Gyn and Obst 1939 LXVIII 45
4 EDWARDS J E Primary reticulum cell sarcoma of the pine report of ca e with autopsy Am Jour Path 1940 XVI 835

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CHAPTER I-E

GIANT FOLLICLE LYMPHOMA AND LYMPHOSARCOMA

By HENRY JACKSON Jr and FREDERIC PARKER Jr

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PART I

GIANT FOLLICLE LYMPHOMA

INTRODUCTION

Giant follicle lymphoma or follicular lymphoblastoma was described first by Brill, Baehr and Rosenthal in 1925, under the noncommittal term "giant lymph follicle hyperplasia."

In 1932 Baehr reported 19 cases and discussed in some detail the clinical findings and the histological picture. At that time, he wrote: "Follow-up observations of 19 cases indicate that the condition is a distinctive form of lymphosarcoma which may manifest more malignant and invasive characteristics later in the disease." Thus, for the first time there arose the suspicion that giant follicle lymphoma might be the prelude to a more serious condition. A similar point of view has been expressed by Sugarbaker and Craver[3] and has been reiterated by Baehr and Klemperer[4]. We agree that the condition is potentially malignant in the sense that it frequently develops into some other and fatal form of malignant lymphoma. Extremely rarely it may be fatal, even though the histological picture has not changed in type. It can never be safely regarded as benign.

PATHOLOGY

The characteristic histological feature of the classic type of giant follicle lymphoma is the tremendous number of huge lymphoid follicles often visible with a hand lens in a fresh specimen or in a stained section. The greatly enlarged follicles virtually fill the entire lymph node, compress the surrounding pulp and not infrequently break through the capsule into the surrounding tissue (Fig. 1). The center of these follicles is filled with actively proliferating cells, either lymphocytes and their predecessors or more rarely reticulum cells. Although occasional polymorphonuclears and monocytes are present also, the uniformity of the predominant cells within the enlarged follicle is notable and important. Sometimes, though not invariably, the enlarged follicles are surrounded by a narrow zone of closely packed mature lymphocytes. Phagocytosis by the reticulum cells does not occur or at most rarely, a point of considerable importance in differentiating this disease from simple inflammatory conditions in which phagocytosis of nuclear

debris and cellular pleomorphism are common Silver stains show strand of reticulum surrounding and outlining the enlarged follicles and demonstrate clearly the compression of the pulp The usual amount of reticulum i seen within the follicles The involved lymph nodes usually are discrete though tho e in the abdomen may become fused into a conglomerate mass

The disease must be differentiated from chronic nonspecific inflammatory conditions of the lymph nodes Uniformity of the cells within the follicles lack of phagocytosis and invasion of the capsule all favor the diagnosis of giant follicle lymphoma It is well to remember also that chronic enlargement of lymph

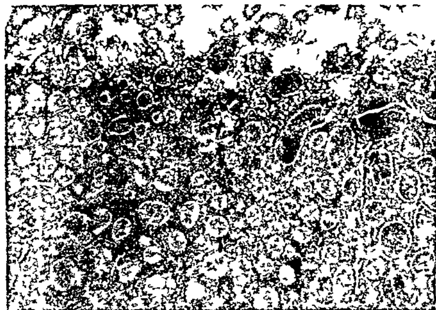


Fig 1 —Giant follicle lymphoma There i increase in size and number of foll cles with exten ion of follicl s into surrounding fat ti ue

nodes in an adult only rarely is due to inflammation alone unless the causative infection is obvious

The lymphadenopathy may be generalized but more commonly appears to be confined e pecially in the early stages of the disease to a comparatively small region Involvement of the retroperitoneal nodes is however common Internal organs such as the spleen are involved occasionally even in the uncomplicated disease Much more rarely there is giant follicle formation in the liver bone marrow breast and other structures

It has been said already that the predominant cell in the enlarged follicles

PART I

GIANT FOLLICLE LYMPHOMA

INTRODUCTION

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In 1932 Baehr reported 10 cases and discussed in some detail the clinical findings and the histological picture. At that time he wrote: "Follow up observations of 10 cases indicate that the condition is a distinctive form of lymphosarcoma which may manifest more malignant and invasive characteristics later in the disease." Thus for the first time there arose the suspicion that giant follicle lymphoma might be the prelude to a more serious condition. A similar point of view has been expressed by Sugarbaker and Craver[3] and has been reiterated by Baehr and Klemperer.[4] We agree that the condition is potentially malignant in the sense that it frequently develops into some other and fatal form of malignant lymphoma. Extremely rarely it may be fatal even though the histological picture has not changed in type. It can never be safely regarded as benign.

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INCIDENCE

Giant follicle lymphoma is most common in middle aged and elderly people though it may be seen at any age (Table I) All of our patients were over 20 years as were Baehr s Baehr reported cases from the age of 20 to 68 with an average age of 42 years Baggenstoss and Heck cite a case of a 2 year old child The rarity in the first decade of life of giant follicle lymphoma in comparison to the occurrence of simple inflammatory conditions of the lymph nodes on the one hand and the occurrence of lymphosarcoma lymphatic leukemia and Hodgkin s granuloma on the other is worth more than passing notice from the diagnostic point of view

TABLE I

GIANT FOLLICLE LYMPHOMA
AGE DISTRIBUTION
39 CASES

Age	Number of Cases
0–9	0
10–19	0
0–9	4
30–39	3
40–49	6
50–59	17
60–69	6
70 79	3

The condition is slightly more common in men than in women

SYMPTOMATOLOGY

The onset is insidious the initial symptom being most commonly painless enlargement of the superficial lymph nodes which are discrete soft or rubbery and non adherent It is worth noting that inguinal lymphadenopathy is far more common early in the disease than in other forms of lymphoma Systemic symptoms such as fever and loss of weight are rare (Table II) though 4 of Baggenstoss and Heck s patients had an initial complaint of weakness

Anemia does not develop unless complications occur to cause anemia and the white blood cell count and the differential cell count are normal unless lymphatic leukemia develops a complication which has been reported although we personally have not seen it

may be the lymphocyte or the reticulum cell Baehr believes that the condition is a form of lymphosarcoma and further states that "in the terminal stage of the disease they have twice observed a marked increase in leukocytes and the appearance of lymphoblasts in the blood stream" It is our experience, too, that in certain cases the condition develops into lymphosarcoma, the type cell then being the lymphocyte or lymphoblast

Similarly though less often there may arise subsequently from the predominant reticulum cells a reticulum cell sarcoma or presumably from the same cell Hodgkin s disease of one or the other type This metamorphosis into a more malignant disease may be seen occasionally in some small portion of an excised lymph node when the patient is first seen or it may occur months or years later, when all histological evidence of the original giant follicle lymphoma has disappeared It is obvious that two or more biopsies or a biopsy and subsequent autopsy are necessary to combat the claims made by some that such changes are fortuitous

In our own series there were 25 cases that at the time of biopsy showed the characteristic histological picture of simple uncomplicated, giant follicle lymphoma as originally described by Baehr Fifteen of these cases remained uncomplicated so far as could be told With the passage of time, however, as proved by subsequent biopsy or autopsy 5 developed Hodgkin s granuloma 1 lymphosarcoma 1 Hodgkin s sarcoma and 1 reticulum cell sarcoma Two patients were lost sight of

Fourteen additional cases showed at the time of first biopsy evidences of transformation into some other type that is, within the node showing the characteristic picture of giant follicle lymphoma there were small areas having the histological features characteristic of some other form of malignant lymphoma In 10 the picture was that of a lymphosarcoma In 2 there was unmistakable evidence of Hodgkin s granuloma and in 1 each were seen the features of reticulum cell sarcoma and Hodgkin s sarcoma In every instance the subsequent course of the disease was that of the particular form of lymphoma evidenced by the first biopsy

Baggenstoss and Heck report 2 cases in which subsequent biopsies revealed the histological picture of lymphosarcoma though "traces of the follicular structure could still be found

It is evident therefore that while giant follicle lymphoma is a comparatively benign condition there is a strong tendency for the condition to become malignant for 28 per cent of our patients eventually developed lymphosarcoma , confirming Baehr s contention that giant follicle lymphoma is a specialized form of that disease and in 29 per cent more one or another form of lymphoma developed

more unusual In a few cases there is loss of weight anorexia or abdominal distress the latter symptom presumably being due to enlargement of retroperitoneal nodes Baehr noted that compression symptoms might occur and further found unilateral exophthalmos in 4 of his 19 cases Baggenstoss and Heck stress the frequency of serous effusions in pleural and peritoneal cavities This complication was found in 6 of our 39 cases So far as our own experience goes in the pure form of giant follicle lymphoma the blood picture remains essentially normal

In short we believe that in patients suffering from the uncomplicated condition such symptoms as they have are due to the presence of painless though often generalized lymphadenopathy It should be emphasized that not infrequently the lymph nodes regress spontaneously for a time and thus lull both the patient and the physician into a false sense of security Such temporary regression even though of comparatively long duration is not uncommon Should some other form of lymphoma develop signs and symptoms of that disease are not slow in appearing and the occurrence of such symptoms and signs such as marked loss of weight hematemesis fever bloody pleurisy with effusion and the like call for a careful reevaluation of the patient s prognosis and treatment

Illustrative Cases

The course of the simple disease is illustrated by the following cases

W G P #13393 This 65 year old man noticed early in 1932 painless swellings in the right neck and right groin These continued with minor exacerbations and remissions until 1934 In December of that year he was admitted to the hospital Physical examination at that time revealed a few olive sized lymph nodes of firm consistence in both sides of the neck and both axillae In either groin were walnut sized discrete non tender rubbery lymph nodes The spleen was readily felt 2 cm below the costal margin Otherwise the physical examination was essentially normal The blood picture was not unusual Biopsy (I S37–1336) showed typical giant follicle lymphoma The patient was given 400 r of x ray to each of the involved areas with complete disappearance of all lymphadenopathy He was alive and well when last seen in October 1942 10 years from the onset of his disease

R Z Py 33 This 21 year old single man noted in November 1933 enlarged painless though rather massive lymph nodes in the right groin There were no other symptoms The nodes were discrete and rubbery The remainder of the physical examination revealed no abnormalities One of the nodes was excised and showed the microscopical picture typical of giant follicle lymphoma He was given approximately 400 r of x ray to the involved area and has remained symptom free to October, 1943

TABLE II

Giant Follicle Lymphoma
Initial Symptoms
39 Cases

	Number of Cases
Inguinal lymphadenopathy	17
Cervical lymphadenopathy	14
Axillary lymphadenopathy	2
Pain in abdomen	2
Edema of l[illegible]	2
Loss of weight	2
Multiple symptom	1

Diagnosis

The disease in its simple and uncomplicated form may be confused with acute and chronic inflammatory lymphadenitis, Hodgkin's disease, tuberculosis, lymphatic leukemia and indeed with any condition causing painless enlargement of superficial lymph nodes without other symptoms of note. It is obvious therefore that the diagnosis can be made only by very careful histological examination of an excised lymph node. In some cases the differential diagnosis between the disease and a simple inflammatory condition may be impossible. Under these circumstances the patient must be watched carefully over a period of time and subsequently biopsies taken if it seems wise. From a clinical point of view the larger the nodes, the more generalized the lymphadenopathy, the more liable the diagnosis of giant follicle lymphoma is to be correct.

Course of Disease

The course of the disease naturally is variable and depends to a large extent upon whether or not the initial simple giant follicle lymphoma is replaced subsequently by some other form of lymphoma.

In those cases showing only uncomplicated giant follicle lymphoma there is usually painless lymphadenopathy, most frequently in the inguinal or cervical regions. The lymph nodes are soft or rubbery, discrete and unattached to the surrounding tissues. Occasionally they are tender. In 1[illegible] of Baehr's 19 cases the spleen was enlarged. Baggenstoss and Heck state that "the spleen is usually greatly enlarged." Splenomegaly in our own experience has been less frequent. Only 4 of 15 cases which apparently remained simple and uncomplicated had during life clinical evidence of enlargement of this organ. Hepatomegaly is still

peripancreatic lymph nodes with metastatic lesions in the trachea, thyroid and kidney and direct extension from the mesenteric nodes to the hepatic flexure of the colon

Another case (C H SD #386) had in 1931 painless enlarged cervical lymph nodes which proved on biopsy to be giant follicle lymphoma (S31–2457) They were treated with moderate doses of x ray, and the patient remained well until 1936 when she reentered the hospital with symptoms consistent with carcinoma of the stomach She died shortly thereafter and the autopsy (A36–449) showed a Hodgkin s granuloma involving the duodenum

We have had but one case in which the disease remained pure giant follicle lymphoma from onset to death

J B B C H #1106907 This 33 year old married man first entered the hospital on November 19 1942 with generalized enlargement of the lymph nodes which were rubbery in consistence freely movable and non tender The largest node measuring 9 x 4 cm was in the right inguinal region There were other nodes about 4 cm in each axilla and in the right supra and infra clavicular regions The liver was 7 cm below the costal margin in the right mid clavicular line extending across the midline and non tender The spleen was 14 cm below the costal margin in the left mid clavicular line Its border was rounded The abdomen was markedly distended and tense Appropriate amounts of high voltage x ray were given to the involved areas and the patient improved greatly

The patient gave a history of symptoms consistent with gastric ulcer In 1941 he noted further painless enlargement in the right inguinal region Three months before entry there was progressive enlargement of the abdomen and marked discomfort after eating For 2 or 3 months he had had marked increase in sweating increasing weakness and fatiguability and increasing dyspnea on exertion

A total of 1 000 r of x ray was given to the spleen and 900 r to each groin between November 24 1942 and January 2, 1943 On December 31 1942 a lymph node removed from the left supraclavicular region was reported as showing giant follicle lymphoma About 2 weeks after irradiation was completed the patient began to improve and was able to be up and about He was discharged after 13 weeks in the hospital

He felt very well for a few weeks and then began having sharp pain in the posterior chest and steady severe pain in the right upper quadrant of the abdomen There was also progressive enlargement of the abdomen dyspnea weakness and sweats He noted no enlargement of the lymph nodes After 3 months at home he was referred back to the hospital because of his poor condition

On this admission examination was essentially the same as before except that the liver was 10 cm below the ribs and its contour appeared to be somewhat

It is evident from what has been said already that giant follicle lymphoma frequently is but a prelude to adventure and that the pathological process frequently becomes altered with the passage of time Under these circumstances it is obvious that there will develop the symptoms and signs of that form of lymphoma into which the disease is progressing Such a train of events is illustrated by the following cases

I P H36-1292 This 54 year old woman was admitted to the hospital in December 1936 The preceding June she had noticed a painless lump in the right axilla Six months later the mass rapidly increased in size and became very tender Under rest and local applications of heat the mass decreased in size and the pain disappeared A biopsy at this time revealed the presence of a typical giant follicle lymphoma (TS37-651) Apparently all the involved lymph nodes were removed The physical examination revealed nothing other than hypertensive heart disease The patient was given 400 r of x ray to the right axilla Except for minor symptoms unrelated to her fundamental disease the patient remained well until March 1939 when on routine physical examination there was found a mass of nodes deep in the right pelvis and in the right groin The patient was given 1 000 r of x ray to the involved areas and remained well until one month later when she complained of much nausea and vomited on several occasions A gastrointestinal series of x rays was entirely negative At this time however an oval lemon sized mass was felt deep in the abdomen just to the right of the umbilicus and for the first time the spleen could be felt just below the costal margin on deep inspiration She was given 1,200 r of x ray to the abdomen and her symptoms disappeared entirely Four months later she returned to the clinic and was obviously very much worse There were enlarged rather soft non tender lymph nodes in either side of the neck The mass to the right of the umbilicus had increased considerably in size A gastrointestinal series of x rays showed an extensive mass pressing upon the hepatic flexure of the colon The patient complained of anorexia dysphagia and fleeting pains deep in the abdomen She had lost 30 pounds in weight The peripheral blood which heretofore had been essentially normal now showed a moderate degree of hypochromic anemia the red blood cell count being 4 000 000 and the hemoglobin 63 per cent The white blood cell picture still remained normal She was given 700 r of x ray to the abdomen and 450 r to the neck There was however no relief from symptoms The abdominal distress continued the dysphagia increased and there developed marked dyspnea with inspiratory stridor This latter symptom increased rapidly and the patient died of asphyxia in October 1939 2½ years after the discovery of the giant follicle lymphoma and 4 months after the rather sudden development of symptoms which proved refractory to x ray therapy

Autopsy showed Hodgkin s sarcoma involving the cervical, mesenteric and

peripancreatic lymph nodes with metastatic lesions in the trachea thyroid and kidney and direct extension from the mesenteric nodes to the hepatic flexure of the colon

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irregular The spleen was 5 cm below the umbilicus No particular change was noted in the lymph nodes

The patient had little appetite he continued uncomfortable from abdominal swelling and sweated a great deal On the 8th hospital day he developed pneumonia and died on the 13th hospital day 6 months after his first hospital admission and approximately 6 years after the onset of giant follicle lymphoma, the only pathological condition other than the pneumonia found at autopsy

Treatment

The treatment of giant follicle lymphoma is prompt irradiation to such therapy the condition responds favorably as Baehr has pointed out

Lymph nodes involved by pure giant follicle lymphoma are commonly very sensitive to x ray and 200 to 400 r to each portal are often sufficient to bring about their complete disappearance Further radiation should be withheld until additional signs and symptoms appear at which time a second biopsy should be done if a superficial lymph node is accessible in order to rule in or out the development of some other form of malignant lymphoma If the disease remain uncomplicated subsequent x ray treatments may be moderate If however by biopsy or clinical evidence it appears that some other type of lymphoma has appeared correspondingly heavier doses should be used It is possible that radical surgical intervention might bring about better results provided the disease process is sharply limited to one readily accessible area though we have no very good evidence that such is the case All foci of infection should be removed if possible

Prognosis

The prognosis of giant follicle lymphoma is varied and depends in large measure on whether the type changes or not So long as the disease remains simple and uncomplicated the outlook is fairly good the average duration being in the neighborhood of 6 years and a small number of cases are alive and free from symptoms as long as 10 years after their initial symptom If however the type changes or complications ensue the prognosis becomes that of the newly developed condition In all cases the prognosis must be guarded Sudden death may occur though it is very rare

BIBLIOGRAPHY

1 BRILL N E BAEHR G and ROSENTHAL N Generalized giant lymph follicle hyperplasia of lymph nodes and spleen Jour Am Med Assoc 19 5 LXXXIV 668

BAEHR G The clinical and pathological picture of follicular lymphoblastoma Trans Assoc Am Phys 193 XLVII 330
3 SUGARBAKER E D and CRAVER L F Lymphosarcoma a study of 196 cases with biopsy Jour Am Med Assoc 1940 CXV 1
4 BAEHR G and KLEMPERER P Giant follicle lymphoblastoma New York State Jour Med 1940 XL ,
5 BAGGENSTOSS A H and HECK F J Follicular lymphoblastoma (giant lymph follicle hyperplasia of lymph nodes and spleen) Am Jour Med Sci 1940 CC 1,

October 1 1944

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BIBLIOGRAPHY

1 BRILL N E BAEHR G and ROSENTHAL N Generalized giant lymph follicle hyperplasia of lymph nodes and spleen Jour Am Med Assoc 19 5 LXXXIV 668

occur The structure of the involved lymph nodes is destroyed and infiltration of the capsule is often present (Fig 2) The reticulum is not increased but represents the normal reticulum of the lymph node The cells in true lymphosarcoma are uniformly round with rather scanty basophilic cytoplasm and a nucleus containing heavy masses of chromatin (Fig 3)

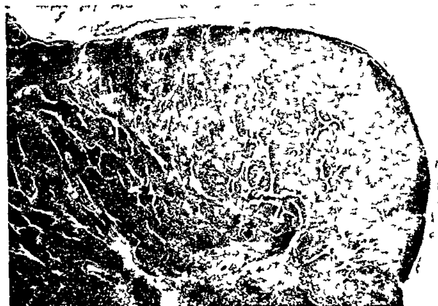


FIG 2 — Lymphosarcoma of a peripheral lymph node There is loss of normal structure of node due to infiltration with tumor cells No follicles are visible and the peripheral sinus is obliterated

Pathological Diagnosis

The greatest difficulty in differential diagnosis is found in distinguishing lymphosarcomas especially the lymphoblastic type from reticulum cell sarcomas In reticulum cell sarcoma the cytoplasm is more abundant irregular in shape frequently amphophilic or acidophilic and occasionally shows evidence of amoeboid activity The nuclei of the reticulum cell sarcoma cells are several times larger than that of an adult lymphocyte irregular in shape and their chromatin finely divided unless the cells are extremely anaplastic While in many instances the diagnosis can be made from an eosin and methylene blue section it should be emphasized that this is by no means always the case and in the last analysi

Part II

LYMPHOSARCOMA

Introduction

Lymphosarcoma, one of the rarest forms of "lymphoma", was described originally by Kundrat[1]. The literature on the subject is extraordinarily confusing. On the one hand the reader often has difficulty in being certain whether a given writer refers to true lymphosarcoma or some other variety of lymphoma and on the other hand certain authors with easy disregard for exact nomenclature and pathological entities include under the term lymphosarcoma many other quite separate and distinct primary diseases of lymph nodes. The situation is confused further by the facts that lymphosarcoma and lymphatic leukemia may coexist in a given patient and that lymphatic leukemia may develop in a patient with lymphosarcoma whose blood previously had been entirely normal. For these reasons only Kundrat's paper has been referred to with full acknowledgment and recognition that there are many other articles of high merit in this field.

Pathology

Lymphosarcoma is a highly malignant invasive tumor composed of mature or immature lymphocytes. We restrict the term lymphosarcoma to those cases which present a single invasive and destructive primary tumor. While invasion of neighboring structures is common, metastases are rare and widespread involvement of the lymphoid tissue is not found with the exception of those cases in which leukemia develops.

Grossly the tumor varies somewhat in appearance. In some instances the lymph nodes can be recognized as such although markedly enlarged; in others their outlines cannot be distinguished. The tumor then appears as a large more or less homogeneous mass of tissue. The color varies from white to pinkish to yellowish. Areas of necrosis are not infrequent. The consistence may be soft or fairly firm.

Histologically the tumor is composed of mature lymphocytes or of lymphoblasts. Mitoses usually are numerous. Neither giant cells nor multinucleated cells

occur The structure of the involved lymph nodes is destroyed and infiltration of the capsule is often present (Fig 2) The reticulum is not increased but represents the normal reticulum of the lymph node The cells in true lymphosarcoma are uniformly round with rather scanty basophilic cytoplasm and a nucleus containing heavy masses of chromatin (Fig 3)



Fig 2 — Lymphosarcoma of a peripheral lymph node There is loss of normal structure of node due to infiltration with tumor cells No follicles are visible and the peripheral sinus is obliterated

Pathological Diagnosis

The greatest difficulty in differential diagnosis is found in distinguishing lymphosarcomas especially the lymphoblastic type from reticulum cell sarcomas In reticulum cell sarcoma the cytoplasm is more abundant irregular in shape frequently amphophilic or acidophilic and occasionally shows evidence of amoeboid activity The nuclei of the reticulum cell sarcoma cells are several times larger than that of an adult lymphocyte irregular in shape and their chromatin finely divided unless the cells are extremely anaplastic While in many instances the diagnosis can be made from an eosin and methylene blue section it should be emphasized that this is by no means always the case, and in the last analysis

the most important and reliable feature by which to make such differentiation is the distribution and amount of reticulum.

In reticulum cell sarcoma the reticulum is greatly increased, occurring as fine strands surrounding groups of cells and individual cells.

In lymphosarcoma, on the other hand, the reticulum is scanty, representing the preexisting reticulum of the lymph node as pointed out above.

As has been said, lymphatic leukemia may develop in a case of lymphosarcoma. This is a frequent event in childhood. It is rare in adults.

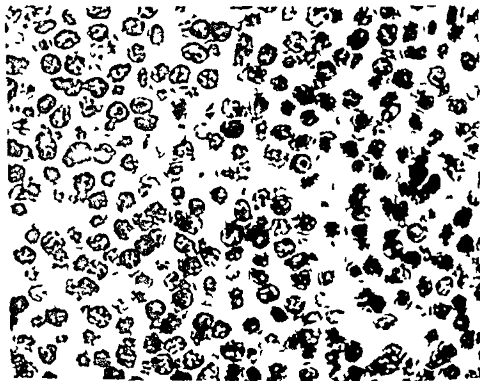


Fig. 3.—Lymphosarcoma. Tumor cells are adult lymphocytes with typical round nuclei and heavy chromatin.

We should like to take occasion here to stress the fact that, in our opinion, the diagnosis of lymphosarcoma cannot be made on a section from a single isolated peripheral lymph node. Histologically the picture is identical with that seen in lymphocytoma with or without leukemia. In order to arrive at a diagnosis it is necessary to know the gross findings as well as the histological appearance of all the organs.

In a series of 10 autopsies on cases of lymphosarcoma among 17,459 autopsies performed in the Boston City Hospital the tumor was primary in the medias

tinal nodes in 6 cases in ca es it was primary in the stomach and in cases in the retroperitoneal nodes In only 1 instance were there distinct metastases and these were to the kidneys from a tumor primary in the mediastinum However involvement of the neighboring structures by extension and invasion by the primary tumor was common (Fig 4) In the mediastinal group the pleura peri



Fig 4 — Lymphosarcoma invadin m ocardium

cardium and diaphragm were invaded frequently The tumors u ually mas ive in size also tended to cause compression of the great ves els The tumors primary in the stomach extended to the regional lymph nodes In the retroperitoneal tumors the pancreas was invaded in both ca es the duodenum in 1 and the bone marrow in 1

During adult life direct extension to neighboring organs is common in the absence of leukemia metastases or wide pread involvement is rare

TABLE I

LYMPHOSARCOMA
ORGANS INVOLVED CLINICALLY
37 ADULT CASES

	Number of Cases
Lymph node	32
Tonsil	11
Mediastinum	15
Gastrointestinal tract	4
Bone	3
Lung	2

It should be particularly noted that the bones and lungs are rarely involved and that on the contrary the tonsil is very often the site of the disease (Table I) This is in sharp contrast to Hodgkin s granuloma

INCIDENCE

The age distribution of lymphosarcoma differs strikingly from that of any other form of malignant lymphoma It is commonest in early childhood and is again found in the later decades It is extremely rare between the ages of 20 and 40 (Table II)

TABLE II

LYMPHOSARCOMA
AGE DISTRIBUTION
67 CASES

Age	Number of Cases
0– 9	8
10–19	12
20–29	0
30–39	1
40–49	4
50–59	8
60 69	[illegible]
70–79	

The disease is definitely more common in males than in females there being 41 males and 26 females in our entire series

SYMPTOMATOLOGY

The initial symptoms are rather strikingly different in the younger and the older patients In childhood petechiae or ecchymoses pallor and enlarged lymph

nodes usually cervical most often were noted first and the initial complaints frequently were multiple

This initial symptomatology probably reflects the frequency with which leukemia is associated with lymphosarcoma in childhood (Table III)

TABLE III

LYMPHOSARCOMA
INITIAL SYMPTOMS DURING CHILDHOOD
30 CASES

	Number of Cases
Petechiae or ecchymoses	22
Pallor	18
Enlarged lymph nodes	16
Splenomegaly or hepatomegaly	8
Skin nodules	6
Weakness anorexia etc	6

In adults the initial symptoms were more varied though far less liable to be multiple (Table IV) Abdominal pain loss of weight anorexia epistaxis vomiting attacks of unconsciousness were seen occasionally The dyspnea may be extreme and it should be noted particularly that persistent sore throat is a not uncommon symptom in elderly people

TABLE IV

LYMPHOSARCOMA
INITIAL SYMPTOMS IN ADULT LIFE
37 CASES

	Number of Cases
Mass in neck	7
Sore throat	5
Cough	4
Dysphagia	4
Dyspnea	3
Weakness	3
Abdominal pain	3
Loss of weight	2
Anorexia epistaxis vomiting unconsciousness	1 each

In children the course is rapid and the symptoms those of an acute form of leukemia plus those of an expansive tumor

As the disease advances in adult life fatigue loss of weight cough sore throat

dyspnea anorexia and abdominal pain become prominent It is noteworthy that in 13 of our 37 adult cases pleurisy with effusion developed, and that in 8 of these the effusion was grossly bloody Bloody ascites developed in 4 of our cases Neither of these complications are common in other forms of malignant lymphoma Fever is not prominent as it is in Hodgkin s granuloma but a large variety of symptoms may develop among them exophthalmos enophthalmos, edema epistaxis hematemesis melena hemoptysis and deafness Only 3 of our adult cases developed leukemia

Unless leukemia develops the peripheral blood picture shows nothing diagnostic or characteristic A moderate degree of anemia usually develops rarely it may be extreme Marked variation in the size and shape of the red cells is not unusual even though there is but slight anemia The percentage of polymorphonuclear leukocytes usually is elevated

Illustrative Cases

The following cases are illustrative of the course of the disease in adult life

A I =P15171 A 17 year old boy was admitted on February 4 1939 Four months prior to entry he began to have a severe cough and increasing dyspnea On one or two occasions he spat up a small amount of blood The dyspnea increased steadily and the cough not infrequently was paroxysmal

On admission to the hospital he was extremely orthopneic and cyanotic By x ray there was marked widening of the mediastinum and a massive bloody effusion in the right chest This was aspirated cautiously and over a period of several days a total of 2,700 c c was removed There were a number of rather firm small nodes in each side of the neck and in each axilla There was marked congestion and slight edema of the face and neck Both the red blood and white blood cell pictures were essentially normal

He was given 800 r of high voltage x ray to the mediastinum and 400 r to each side of the neck The response was dramatic and he was discharged a month after admission The mediastinal mass as well as the effusion had practically disappeared and the patient felt well

A month later however in April 1939 he was readmitted for extreme weakness and dyspnea The mediastinal nodes once more were markedly enlarged, and again there was pleural effusion His blood picture remained essentially normal He was given 800 r of x ray to the mediastinum with appreciable shrinking of the mass but with little amelioration of his weakness which remained extreme Further x ray therapy produced no apparent benefit

In June 1939 four months after entry the patient s white blood cell count suddenly rose to 51 000 and coincidentally the percentage of lymphocytes rose

to 79 He had numerous nose bleeds The white cell blood count increased to 104 000 The red blood cell count fell to 1 700 000, and the patient died June 29 1939 8 months after the first symptoms properly attributable to his disease

T L, H_{3}0–385 A 75 year old man was admitted to the hospital on March 6 1930 Six months previously he noticed a growth on his right tonsil The mass gradually increased in size and 2 weeks before entry it became definitely painful There were no other physical findings worthy of note

He was given 1 00 r of x ray to the right side of the neck and thereafter the lymph nodes disappeared and the tonsillar mass diminished greatly in size Three months later however a mass of rather soft lymph nodes appeared in the right neck and several nodes were found in the right axilla and the spleen was felt 4 cm below the costal margin These responded well to x ray therapy but 6 months later all reappeared

In spite of repeated doses of high voltage x ray the nodes continued to increase in size and the patient became rapidly weaker

He died suddenly on May 10 1931 one year and 9 months after his first symptom

Course and Treatment

The course of the disease is almost always progressive to death Great alleviation of symptoms and marked improvement in health may follow x ray therapy The results however are but transitory and it often seems that the more favorable the initial treatment the sooner the disease will return

Aside from appropriate high voltage x ray 400 to 1 600 r at proper intervals there is little to be offered other than symptomatic relief Transfusions are of course indicated if the red blood cell count falls, or if a bleeding tendency develops as it so frequently does in children

The question of radical surgery is a moot one We have never seen a case suitable for such therapy There are a number of reports of successful excision of a localized lymphosarcoma and radical surgery might well be indicated in certain cases though a careful scrutiny of the case reports in the literature leaves some doubt as to whether these patients had lymphosarcoma or reticulum cell sarcoma the latter a condition in which we do believe that radical surgery may rarely result in a cure

Prognosis

Lymphosarcoma kills rapidly especially in childhood No case under 12 years of age lived more than 8 months most were dead in 4 months In the older age groups an occasional case will live 3 or even 4 years from onset (Table V)

dyspnea anorexia and abdominal pain become prominent It is noteworthy that in 13 of our 37 adult cases pleurisy with effusion developed and that in 8 of these the effusion was grossly bloody Bloody ascites developed in 4 of our cases Neither of these complications are common in other forms of malignant lymphoma Fever is not prominent as it is in Hodgkin s granuloma, but a large variety of symptoms may develop among them exophthalmos enophthalmos, edema epistaxis hematemesis melena hemoptysis and deafness Only 3 of our adult cases developed leukemia

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CHAPTER II

THE THYMUS AND STATUS LYMPHATICUS

By DAVID HISMAN AND STANLEY E HARRIS

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EMBRYOLOGY AND ANATOMY

The thymus proper originates as an endodermic structure derived from the ventral wall of the third pair of pharyngeal pouches and to a lesser extent from the fourth It consists at birth of a glandular organ surrounded by a fibrous capsule which sends its prolongations among the lobules It is triangular and relatively broad with the base resting on the pericardium Thickest above it descends in front of the pericardium in two more or less distinct flattened lobes It is in contact in the anterior mediastinum with a large part of the arch of the aorta and is grooved on its posterior surface by the innominate veins and the superior vena cava Above it may reach the trachea and esophagus laterally it extends between the pericardium and the pleura Occasionally aberrant thymus tissue is found in the cervical region often associated with the thyroid gland At birth the thymus weighs twelve or thirteen grams It gradually increases in size until it reaches its maximum weight of from thirty two to thirty seven grams at fifteen years of age thereafter it undergoes a

TABLE V

Lymphosarcoma
Duration from Onset to Death
67 Cases

Age	Duration (Months)	Average Duration (Months)
0 15	1–8	5
16–40	2–30	5
41–75	1 30	17

It is well to remember that as in other forms of malignant lymphoma sudden death may ensue even though the patient appears to be in comparatively good health

One cannot discuss the subject of lymphosarcoma without a word concerning the so called *lymphocytoma* in which isolated lymph nodes often of considerable size are infiltrated and destroyed by adult lymphocytes We have seen a number of such cases all have either died within a comparatively short time of some unrelated disease or have developed lymphatic leukemia

BIBLIOGRAPHY

1 KUNDRAT H Ueber Lymphosarkomatosis Wien klin Wochnschr 1893 VI 11
October 1 1944

in young children produced no serious sequelæ Thymectomy in the young has led to divergent results possibly due to the difficulty of completely extirpating the thymus in many experimental animals Basch[3] Soli[4] Nitschke and others believed the gland influenced calcification of bone Klose and Vogt[6] found that about fourteen days after its removal young puppies became adipose sluggish stupid and easily fatigued later in spite of eating enormously they lost weight the bones became soft and finally after several month the animals died These findings were not confirmed by other authors Park and McClure[7] in an excellent critical review of the literature in 1919 concluded that inferences drawn from the experimental work of many investigators were subject to question Their own investigations led to negative results Marine and Manley[8] believed that thymectomy hastened sexual maturity Soli[9] demonstrated that some hens whose thymus glands had been removed when they were chicks laid eggs without shells and concluded that the thymus had some relation to calcium metabolism Andersen[10] found that thymectomy did not affect the age or weight at which female rats reached puberty nor the age at onset of the estrus cycles that it did not affect the actual or relative weight of the thyroid adrenal or spleen at five months of age and that the growth appearance or behavior of young rats was unchanged by thymectomy

Recently Einhorn and Rowntree[11] have confirmed many of these findings However they showed that in the offspring of thymectomized rats a definite retardation in growth occurred during the first six weeks of life the subsequent growth being normal and that thymectomy in successive generations of parents resulted in progressive retardation in the rate of growth of the offspring The same results were obtained when the young were nursed by control foster mothers showing that the changes were not brought about through the milk There was some evidence of retarded sexual development since in two females of the third generation estrus did not become regular until after the second and fourth cycles respectively When thymectomized rats of successive generations were given daily injections of thymus extract the growth curves coincided closely with those of control animals

Another method of study has been that of administering gland tissue or its extracts to normal or thymectomized animals Cudernatsch[1] fed thymus to tadpoles and found that they grew to be very large without undergoing metamorphosis Uhlenhuth[13] confirmed this finding but explained it on a nutritional basis Groebbels[14] concluded that the effect of enriching the food of vitamin starved tadpoles with thymus was a non specific stimulus rather than that of a hormone since the same results could be produced by feeding testicular substance Swingle[1] failed to obtain any results and concluded that the effects noted by Cudernatsch were attributable to some other factor than thymus

gradual involution At birth the gland consists of a cortex and medulla of about equal size The cortical substance histologically resembles dense lymphoid tissue The medulla consists of a supporting framework of branching cells within the meshes of which lie small mononuclear lymphocytes occasional eosinophiles along the blood vessels, and multinuclear giant cells Numerous spherical or elliptical masses (012 to 1 mm or more in diameter) of concentrically disposed flattened modified cells, known as Hassall s corpuscles are found in the medulla According to His Stieda Hammar and Maximow the reticulum and Hassall s corpuscles are derived from the epithelial anlage the small thymic cells and eosinophiles arise in the mesenchyme and migrate into the gland This view is accepted by most authorities but not by all, and it must be said that the origin of the various cells found in the thymus is as yet unsettled The arteries spring chiefly from the internal mammaries but small branches may come from the thyroid and pericardial arteries The cortex is provided with a rich capillary network while the medulla is relatively poorly supplied The veins between the lobules converge to form larger trunks running in many directions the most important emptying into the left innominate The lymphatics are large and numerous and empty into nodes behind the sternum The nerves are small and are derived from the sympathetics and the vagus they end chiefly in the walls of the blood vessels After puberty the gland atrophies its elements being easily overlooked in the mediastinal fat in later life The corpuscles of Hassall are large and plentiful between eighteen and thirty years but with advancing age they become fewer in number smaller in size and are sclerosed or calcified in aged subjects A comprehensive review of the literature and discussion of the anatomy of the thymus may be found in J Aug Hammar s recent monograph Die normal morphologische Thymusforschung im letzten Vierteljahrhundert Analyse und Synthese nebst einigen Worten zu der Funktion frage Leipzig 1936

PHYSIOLOGY

Study of the physiology of the thymus generally has been pursued along lines found to be successful in determining the functions of various endocrine glands but until recently research was so unfruitful that as late as 1930 a standard textbook of physiology[1] stated in summary that "It is very doubtful whether the thymus should be counted as one of the endocrine organs" In 1858 Friedleben concluded from his experiments that it was concerned with growth with nutrition and with blood formation, but that it was not indispensable to life Extirpation of the gland by numerous investigators since then has demonstrated that its removal in young animals is not incompatible with life while surgical removal or x ray destruction of the thymus in a few instances

in young children produced no serious sequelæ. Thymectomy in the young has led to divergent results, possibly due to the difficulty of completely extirpating the thymus in many experimental animals. Basch[3] Soli[4] Nitschke and others believed the gland influenced calcification of bone. Klose and Vogt[6] found that about fourteen days after its removal young puppies became adipose, sluggish, stupid and easily fatigued; later in spite of eating enormously they lost weight, the bones became soft, and finally after several months the animals died. These findings were not confirmed by other authors. Park and McClure[7] in an excellent critical review of the literature in 1919 concluded that inferences drawn from the experimental work of many investigators were subject to question. Their own investigations led to negative results. Marine and Manley[8] believed that thymectomy hastened sexual maturity. Soli[9] demonstrated that some hens whose thymus glands had been removed when they were chicks laid eggs without shells and concluded that the thymus had some relation to calcium metabolism. Andersen[10] found that thymectomy did not affect the age or weight at which female rats reached puberty nor the age at onset of the estrus cycles; that it did not affect the actual or relative weight of the thyroid, adrenal or spleen at five months of age; and that the growth, appearance or behavior of young rats was unchanged by thymectomy.

Recently Einhorn and Rowntree[11] have confirmed many of these findings. However, they showed that in the offspring of thymectomized rats a definite retardation in growth occurred during the first six weeks of life, the subsequent growth being normal, and that thymectomy in successive generations of parents resulted in progressive retardation in the rate of growth of the offspring. The same results were obtained when the young were nursed by control foster mothers, showing that the changes were not brought about through the milk. There was some evidence of retarded sexual development, since in two females of the third generation estrus did not become regular until after the second and fourth cycles respectively. When thymectomized rats of successive generations were given daily injections of thymus extract, the growth curves coincided closely with those of control animals.

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feeding After feeding thymus substance to rats, Hewer[16] found that sexual maturity was delayed that feeding the parents caused marked delay in sexual maturity in the offspring of both male and female but that the gestation period of the offspring was not altered Hoskins[17], however, found normal development of the sexual organs of rats to which thymus had been fed Riddle[18] mixed thymus gland with the food of pigeons having small thymuses who were laying eggs deficient in shell and albumin, and found that subsequently they laid normal eggs leading him to the belief that a thymus hormone controls the secretion of the eggshell Later work by Riddle and Krizenecky[19] and by Greenwood[20] cast doubt on these conclusions In general the results of feeding experiments have been inconclusive and to some extent contradictory, although in many growth and development appeared to be stimulated Groebbels found that when thymus was mixed with the food of fishes they grew 2 to 3 times as fast as the controls although in some instances they consumed less food In another experiment when thymus was fed to viviparous toothed carp they showed a distinct increase in the number and size of the litters In 1925 Schazillo[22] demonstrated that in tissue cultures thymus as well as lymphocyte extract was rich in growth promoting substance Recently Mendeleeff[23] found that thymus juice stimulated the growth of the epithelial and not of the fibroblastic elements of guinea pig embryo cultures

Extracts of the thymus prepared by various methods have been injected into experimental animals with results which have not been entirely conclusive Nitschke[24] isolated two substances having different characteristics from an extract of calves thymus One when injected into puppies produced a fall in serum calcium with the development of the typical clinical picture of tetany and death in the course of 24 to 48 hours The other substance produced a drop in serum inorganic phosphorus These substances were present also in extracts of other organs rich in lymphocytes namely, the spleen and lymph nodes, but not in extracts of liver kidney or muscle Nitschke[25] also isolated a substance from the urine of ten spasmophilic infants which reproduced the spasmophilic syndrome low serum calcium increased response to electrical stimulation convulsions and death when injected subcutaneously in puppies This substance was not found in the urine of 11 normal infants nor in that of three of the cases of tetany after recovery He proposed the theory that tetany in babies is due to hyperfunction of the lymphocytic system and further that this system elaborates a hormone antagonistic to that of the parathyroids in relation to calcium metabolism When other animals than puppies were used however the findings were inconclusive

For several years an extract called thymocrescin has been under investigation in Asher's laboratory The preparation has been purified till 1 mg is effective[26] Solutions of this substance give the peptid reaction Its

principal effect is that of stimulating growth Nowinski[77] found that vitamin starved rats gained weight rapidly when daily subcutaneous injections of 20 mg of thymocrescin were given Asher gave daily injections of thymocrescin to one of two groups of rats fed on MacCollum s vitamin D free diet Not even microscopic evidence of rickets was found in this group while severe rickets was produced in the controls Nowinski[78] found that the thymus contains at least two active substances one water soluble thymocrescin and another which is soluble in alcohol He also concluded that thymocrescin influences gonadal development A similarity between thymocrescin and the growth promoting fraction of the vitamin B complex has been noted Bachmann[79] found that thymocrescin failed to prevent or postpone death in rats on a vitamin B free diet but the animals which had received daily injections of 1 mg of this preparation weighed significantly more about 20 per cent at time of death than the controls Asher concluded that the growth promoting principle of the thymus is a true hormone which acts as a regulator of growth like the thyroid and gonads and unlike that of the anterior lobe of the hypophysis which induces abnormal growth when present in excess He believed that thymocrescin represents this substance and pointed to the minuteness of the effective dose in support of his contention Hammar[80] however pointed out that a small quantity of vitamin is also potent and concluded that the nature of thymocrescin has not been determined

Using an extract produced by Hanson Rowntree and his coworkers[81] since 1933 have obtained results in rats which not only have thrown light upon the functions of the thymus but have opened a new field of biologic research namely the study of the effects upon successive generations of offspring through treatment of the parents

The original Hanson preparation used was made by acid extraction with the aid of heat of the thymus glands from 2 to 6 weeks old calves While most of the extract thus prepared was found to be active a certain variability was noted Chemical studies revealed that all potent batches of the extract contained an iodine reducing substance while in non potent extracts this substance was lacking The method of extraction later was modified and at present the preparations employed by Rowntree and his associates are roughly standardized on the basis of their iodine reducing content Extracts active in promoting growth have been found to contain glutathione ascorbic acid and cysteine[82] further research is under way

Daily intraperitoneal injections of 1 cc of thymus extract were given to a series of white rats of a well known strain As their offspring reached a suitable age they were mated and likewise injected This was carried out through succeeding generations and both parents and offspring were studied and compared with control animals of the same strain The results were so startling

feeding After feeding thymus substance to rats, Hewer[16] found that sexual maturity was delayed that feeding the parents caused marked delay in sexual maturity in the offspring of both male and female but that the gestation period of the offspring was not altered Hoskins[17], however found normal development of the sexual organs of rats to which thymus had been fed Riddle[18] mixed thymus gland with the food of pigeons having small thymuses, who were laying eggs deficient in shell and albumin and found that subsequently they laid normal eggs leading him to the belief that a thymus hormone controls the secretion of the eggshell Later work by Riddle and Krizenecky[19] and by Greenwood[20] cast doubt on these conclusions In general the results of feeding experiments have been inconclusive and to some extent contradictory, although in many growth and development appeared to be stimulated Groebbels[1] found that when thymus was mixed with the food of fishes they grew to 3 times as fast as the controls although in some instances they consumed less food In another experiment when thymus was fed to viviparous toothed carp they showed a distinct increase in the number and size of the litters In 1925 Schazillo[22] demonstrated that in tissue cultures thymus as well as lymphocyte extract was rich in growth promoting substance Recently Mendeleeff[23] found that thymus juice stimulated the growth of the epithelial and not of the fibroblastic elements of guinea pig embryo cultures

Extracts of the thymus prepared by various methods have been injected into experimental animals with results which have not been entirely conclusive Nitschke[4] isolated two substances having different characteristics from an extract of calves thymus One when injected into puppies produced a fall in serum calcium with the development of the typical clinical picture of tetany and death in the course of 24 to 48 hours The other substance produced a drop in serum inorganic phosphorus These substances were present also in extracts of other organs rich in lymphocytes namely the spleen and lymph nodes but not in extracts of liver kidney or muscle Nitschke also isolated a substance from the urine of ten spasmophilic infants which reproduced the spasmophilic syndrome low serum calcium increased response to electrical stimulation convulsions and death when injected subcutaneously in puppies This substance was not found in the urine of 11 normal infants nor in that of three of the cases of tetany after recovery He proposed the theory that tetany in babies is due to hyperfunction of the lymphocytic system and further that this system elaborates a hormone antagonistic to that of the parathyroids in relation to calcium metabolism When other animals than puppies were used however the findings were inconclusive

For several years an extract called ' thymocrescin has been under investigation in Asher s laboratory The preparation has been purified till 1 mg is effective[25] Solutions of this substance give the peptid reaction Its

the testicles was greater than normal On repeating the experiment however the change often was found to be insignificant Seckel[34] noted a retention of water and calcium in the majority of infants after subcutaneous injection of an albumin free thymus extract Recently Roboz[35] treated 20 marasmic infants with injections of an aqueous thymus extract Six were cured and 8 showed improvement the favorable results being attributed to an increased capacity of the cells to retain water Kostyál[36] concluded from his work with infants suffering from dysentery that the thymus is the primary gland controlling water secretion

Implantation experiments have been carried out until recently with negative results Marine and Manley and others have shown that implants can be made to survive and to grow Recently Einhorn and Rowntree[37] have studied the biological effects of homologous implants in successive generations of rats It was found that when thymus tissue obtained from stock rats between the ages of o and 50 days was implanted subcutaneously in different sites on the back and neck of numerous rats about two-thirds of the grafts took and later were absorbed disappearing grossly in about two weeks No effect was apparent in the first generation the litters were large and the offspring at birth were strong and of good size In successive generations accruing precocity in growth and development occurred when repeated implantations were continued These changes were greatest in the fourth generation and while quantitatively less marked than those noted following daily injection of thymus extract qualitatively they were identical in every respect This work is as yet incomplete but results already obtained appear to be of considerable value in confirming the findings which were noted in their injection experiments

Hammar suggests that the thymus may act in early life as a central organ or storehouse for a growth promoting substance (vitamin?) which function later is transferred to the testicles and ovaries He is convinced that the functional unit of the thymus is the Hassall corpuscle while Dustin believes it to be the thymocyte Cramer Drew and Mottram[38] have suggested that the transmission of vitamin B to the body cells is a specific function of the lymphocytes The absence of a rich capillary network about Hassall s corpuscles and the abundance of small round cells (lymphocytes?) in the thymus have led to the supposition that the thymic secretion may be transported by these cells This question together with many others still is unsettled

The effects upon the thymus of extirpation of other glands has been studied also but the results have not been conclusive Calzolari[39] removed the testes of young rabbits and found a delay in the involution of the thymus This was confirmed by Henderson[40] Goodall[41] and Gellin[42] but Paton[43] obtained negative results Marine Manley and Baumann[44] showed that suprarenalectomy in rabbits prevents involution and may cause regeneration of a highly

that they were repeated and since then have been carried out to the tenth generation In all cases the effects of treatment have been the same When administered to new born rats of untreated parents very little effect on growth and development was noted However, the offspring of treated rats showed a striking and accruing precocity following continuous injections of successive generations In the tenth generation the average birth weight was 6 gm (control 4 6) the ears were open and the teeth were present at the first inspection (controls ears open in 2½–3½ days and teeth erupted in 8–10 days) hair appeared in six hours (controls 12–16 days), the eyes were opened in 36–40 hours (controls 14–17 days) the testes had descended by the third day (controls 31–40 days) the vagina was open on the sixth day (controls 55–72 days) and vaginal smears indicated that estrus followed within three days Psychic precocity in the treated series of rats was no less striking than the physical Rats of the fifth to tenth generation at –3 days of age were as alert and active as control animals of 10 20 days Weaning was possible as early as 48 hours The young rats would then find their own food and water run about nest burrow under excelsior or climb up the wire netting of their cages as well as control rats four or five times their age Rats of the advanced generations could swim as early as the third day In the successive generations of treated rats however development was only affected during early life especially before the sixteenth day Giants did not develop and in later life they showed no manifestations not seen in control rats The original pair of thymus treated animals were living after 25 months having seen their descendants to the tenth generation It is interesting to note that interruption of thymus administration for one generation nullified in the offspring either completely or to a large extent the effects of treatment even if it had been carried through several preceding generations Just as precocity was found to be lacking in early litters of thymus treated rats the absence of thymus effect was more marked in succeeding litters cast after its discontinuance The results obtained by Rowntree and his associates when the extract was administered by mouth, were inconclusive

Toxic effects were never noted unless the extract was given in excessive doses Large amounts of the extract given intraperitoneally produced auriculo ventricular dissociation with eventual death from heart block It is not clear whether this was a thymu effect or whether it was produced by some other substance present in the extract

A relationship of the thymus to water metabolism is suggested by the work of several investigators Parhon Cahane and Marza[33] found that in thymectomized guinea pigs there is a definite and at times a considerable decrease in the water content of most organs except the adrenals and the muscles while in the animals with hypertrophied thymuses the water content of most organs except

the testicles was greater than normal. On repeating the experiment, however, the change often was found to be insignificant. Seckel[34] noted a retention of water and calcium in the majority of infants after subcutaneous injection of an albumin free thymus extract. Recently Roboz[35] treated 20 marasmic infants with injections of an aqueous thymus extract. Six were cured and 8 showed improvement, the favorable results being attributed to an increased capacity of the cells to retain water. Kostyál[36] concluded from his work with infants suffering from dysentery that the thymus is the primary gland controlling water secretion.

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glands have been observed at all ages Histological studies have led to the conclusion that these sudden fluctuations are due chiefly to multiplication of the small thymic cells or by immigration of lymphocytes which they closely resemble and to their rapid destruction or emigration The rapid growth which occurs during the first two years of life results from parenchymal enlargement subsequent increase in weight is due largely to growth of the interlobar stroma (Hammar) Following puberty the parenchyma shrinks rapidly for 4 or 5 years largely through decrease in number of the small thymic cells Thereafter the parenchymal reduction occurs more gradually and is accompanied by a decrease in volume of the medulla both through destruction of the reticular cells and through a slowing of their rate of division However Hammar states that throughout life new small thymic cells reticular cells and Hassall s corpuscles are being formed but at a much slower rate At any time during life the normal processes may be reversed or accelerated resulting in more or less rapid hypertrophy or involution The factors leading to all these changes are obscure From the conflicting statements and speculation with which an extensive literature is rife can only be gleaned the impression that they are influenced by the state of bodily nutrition and by the interactions of the internal secretions of at least the thyroid the suprarenal the hypophysis and the gonads

Accidental or Pathological Involution — This may occur rapidly and at any age during acute or chronic infections various intoxications periods of inanition pregnancy and following irradiation The cortex diminishes in size more rapidly and to a greater degree than the medulla the small thymic cells emigrating and being destroyed in large numbers At times the gland may shrink within a week to one fifth of its former size Pathological involution may be followed by rapid regeneration

Enlargement of Thymus and Conditions Associated with It

The anatomic causes of thymic enlargement are hypertrophy or hyperplasia tumors and cysts

Hypertrophy and Hyperplasia

As has been stated above the size of the thymus fluctuates during life in response to influences which at present are not understood Only when growth or hypertrophy occurs with unusual rapidity in relation to age or when the gland greatly exceeds that expected for the age of the individual can it be considered abnormal Pathological hypertrophy may take place at any age When present in infancy periodic attacks of laryngeal stridor dyspnea and cyanosis thymic asthma may occur sometimes with a fatal termination

involuted gland and even thymic hypertrophy These results were confirmed by Jaffe[4] The former authors found suprarenalectomy plus gonadectomy to be a more powerful stimulus for thymus and lymphoid regeneration than either of these procedures alone In their experiments Scott and Bradford[46] found that prolonged treatment with extract of the adrenal cortex resulted in hypertrophy of the thymus and conversely that removal of the thymus was followed by hypertrophy of the adrenal cortex Thyroidectomy in rabbits appeared to hasten involution of the gland in the experiments of Jeandelize Lucien and Pariosot[47] and of Marine Manley and Baumann, the same results followed hypophysectomy the gland undergoing premature involution Recent work of Rowntree and his associates[48] with pineal extract seems to show that this gland acts antagonistically or in the opposite direction to the thymus

In summary the thymus has been shown to contain one or more substances having a stimulative effect upon growth and development of experimental animals during early life Thymic extracts of considerable potency in promoting growth have been made notably by Asher (thymocrescin) and by Hanson Rowntree and their associates Rowntree s work has demonstrated that his extract produces precocious development of the offspring following daily injections into parent rats and that the effects are cumulative in successive generations as long as treatment is continued and conversely that thymectomy in successive generations results in cumulative retardation of growth and development It has not been established that these substances are specific secretions of the gland Opinion is divided as to whether the growth stimulating factor found in the thymus is a hormone a vitamin or some other substance A relationship between the thymus and undoubted endocrine organs such as the gonads the hypophysis the thyroid and the adrenals has not yet been established although there is some suggestive evidence of such a connection

Growth and Involution

The only norm which has been established concerning the size of the thymus is that in relation to age and as Hammar has repeatedly emphasized this standard is of little value since it is the quantity of parenchyma alone which is important and how much parenchyma represents the top normal at a given age is unknown The figures given by Friedleben Hammar von Sury Schridde Bratton and others represent the average weights of whole gland in relation to age and are necessarily inexact A wide normal range is accepted by all authorities especially during the years before puberty In general the size of the thymus in infancy is proportionate to the body weight[49] and to the development of the lymphoid tissues[50] Rapid changes in the size of apparently norma

gland have been observed at all ages Histological studies have led to the conclusion that these sudden fluctuations are due chiefly to multiplication of the small thymic cells or by immigration of lymphocytes which they closely resemble and to their rapid destruction or emigration The rapid growth which occurs during the first two years of life results from parenchymal enlargement subsequent increase in weight is due largely to growth of the interlobar stroma (Hammar) Following puberty the parenchyma shrinks rapidly for 4 or 5 years largely through decrease in number of the small thymic cells Thereafter the parenchymal reduction occurs more gradually and is accompanied by a decrease in volume of the medulla both through destruction of the reticular cells and through a slowing of their rate of division However Hammar states that throughout life new small thymic cells reticular cells and Hassall s corpuscles are being formed but at a much slower rate At any time during life the normal processes may be reversed or accelerated resulting in more or less rapid hypertrophy or involution The factors leading to all these changes are obscure From the conflicting statements and speculation with which an extensive literature is rife can only be gleaned the impression that they are influenced by the state of bodily nutrition and by the interactions of the internal secretions of at least the thyroid the suprarenal the hypophysis and the gonads

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Irradiation over the thymus gives relief and often prevents recurrence In adults hypertrophy or hyperplasia is found in association with other conditions in particular status lymphaticus, myasthenia gravis, Graves disease, Addison's disease, Hodgkin s disease leukemia and hemophilia

Status Lymphaticus

The occurrence of sudden death has been a powerful stimulus to research ever since man ceased to be satisfied with the explanation that such tragedies are caused by a visitation of God ' In reporting the sudden death without adequate cause of a five months old boy Felix Plater in 1614[51] recorded in the autopsy findings an enlarged thymus In the eighteenth century Morgagni, Bichat and others noted the association of thymic enlargement with sudden death It was not till 1830 however that Kopp drew attention to the fact that a hyperplastic thymus frequently was the only pathological condition found in cases where sudden death had occurred in infants during attacks of laryngeal stridor dyspnea hoarseness, a brassy cough and cyanosis He advanced the view that death was due to pressure of the enlarged thymus upon the trachea and other mediastinal structures and applied the term asthma thymicum to the condition This explanation enjoyed general acceptance till 1858 when Friedleben published his observations and denied that death in these cases could be due to mechanical pressure of an enlarged thymus and that there was no such thing as thymic asthma Es gibt kein Asthma Thymicum A heated controversy thus was precipitated and its echoes have not yet died from the literature

In 1889 Paltauf[43] began a series of publications which together with those of others of the Vienna school soon established the concept of the status lymphaticus as a constitutional anomaly characterized by generalized lymphoid hyperplasia a persistent or hyperplastic thymus, hypoplasia of the cardiovascular system and a tendency to sudden death through the inability of persons with this anomaly to withstand shocks or injuries that would not seriously affect normal individuals This view came to be accepted by the majority and the concept has been further widened in an extensive literature which has developed The part played by the thymus still is in doubt Some consider thymic hyperplasia as an important element in the syndrome, others as merely incidental Shades of opinion are reflected in the variety of terms used to designate this specific constitutional anomaly some of the most commonly used being status thymicus status thymicolymphaticus status lymphaticus or constitutio lymphatica and status hypoplasticus Some deny that such a condition exists Recently a British Commission obtained only negative findings from a careful study of histological sections and pathological data from supposed

cases of status lymphaticus occurring in various parts of the British Empire and recommended that the subject be withdrawn from further consideration. The majority of clinicians however are agreed that a recognizable not infrequently encountered specific constitutional anomaly exists to which for want of a better designation one of the above terms is applied.

From the pathological standpoint many agree with Hammar that there is no essential histological difference between the thymus of status lymphaticus and that of a normal individual. Others notably Bartel Schridde Hart and Symmers[54] believe that more or less characteristic changes occur in the thymus and other organs. In 4 000 autopsies at Bellevue Hospital Symmers[54] noted status lymphaticus 249 times or 6 2 per cent. Of these 118 were status lymphaticus proper 89 were of the recessive type while 42 cases fell into the borderline group where hyperplasia and atrophy were found in different places in the lymphoid tissues. In all well developed cases the thymus gland was hyperplastic. The largest gland encountered weighed 115 gm. The youngest subject was a child of eight hours in whom death had occurred suddenly. The thymus weighed 70 gm. The same weight was recorded for the thymus of the oldest case an acromegalic patient of 38 years whose death was due to an intercurrent infection. The faucial lingual and pharyngeal tonsils were hyperplastic in about 50 per cent of the 118 cases and the follicles of the intestinal tract in 88 per cent. In 88 per cent the spleen was rich in hyperplastic lymphoid follicles but showed no gross enlargement. No changes were noted in the mesenteric axillary inguinal cervical and peribronchial lymph nodes. Histologically the principal change observed in the well developed cases was hyperplasia of the cortical lymphoid follicles and in some the blood sinuses in the thymus were very large and contained greatly increased numbers of lymphocytes. In many cases especially in subjects who had met death suddenly and in response to apparently trivial provocation certain degenerative changes were found in the germinal follicles of the lymphoid structures which Symmers considers as characteristic of status lymphaticus. These changes he believes point to liberation of nucleoproteids and support the theory that death occurs through anaphylaxis in an individual sensitized as a result of destruction of innumerable germinal follicles. The proportion of males to females in this series was as 6 1.

Clinical Diagnosis — To establish diagnostic criteria to assist the clinician in recognizing the condition during life has been the aim of many authors notably Escherich[55] von Neusser Symmers Emerson and Norris. The task has not been easy since all degrees of status lymphaticus may exist at all ages and since the condition is not a fixed one tending to become less marked as age advances. In well developed cases the typical picture is fairly characteristic. In childhood the body is delicately molded slender and graceful the skin is

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contraindication to an elective operation A relative lymphocytosis which is a frequent feature of the status lymphaticus is thought by many to increase seriously the surgical risk and operation is avoided in such cases or is performed with increased caution Administration of antitoxin intravenous medication and the so-called shock therapy may result in sudden death when status lymphaticus is present

Emotional instability and such conditions as addiction to alcohol cocaine heroin and morphine are said to be noted more frequently in persons showing lymphoid characteristics than in others Emerson found that 22 per cent of 1 000 cases suffering from the effects of attempted suicide or drug addiction showed the physical stigmata of status lymphaticus At autopsy 80 5 per cent of 52 cases of suicide examined by Bartels and Miloslavich[6] showed signs of this condition Among the insane and epileptics status lymphaticus is seen frequently

Cerebral hemorrhage occurring in young non syphilitic subjects while uncommon is seen chiefly in those having a lymphatic constitution The fatal rupture may occur as the result of a fall or of a blow which ordinarily would not cause serious injury Such accidents are due to the hypoplasia of the small blood vessels of the brain found in this condition This defect in the cerebral vascular system is believed by Symmers[4] to account for the fact that the five deaths from caisson disease recorded at Bellevue Hospital all occurred in men of this constitution

Cause of Death —That cardiac arrest is the immediate cause of death in status lymphaticus has long been known How this is induced however is obscure The early theory that pressure of an enlarged thymus upon the trachea blood vessels and nerve trunks is responsible has been disputed In its favor are cited the frequent finding in infants subject to attacks of laryngeal spasm of an enlarged thymus shadow on x ray examination the observation of Jackson[5] and others through direct bronchoscopic examination of tracheal compression by an enlarged thymus and occasional postmortem evidence of tracheostenosis On the other hand elaborate studies by von Sury[8] Tamassia Schoeppler[9] and others have shown that a degree of tracheal compression necessary to cause death could not have been exerted by the large thymus removed at autopsy Even thymic pressure as the cause of laryngeal stridor has been questioned increasingly The relief produced in infants suffering from these attacks by irradiation which formerly was attributed to reduction of the size of the thymus through the destructive effects of the x rays often appears too rapidly to be thus explained It may be due to other effects of the roentgen rays In this connection a recent report by Nesbit[60] is of interest He noted that 28 infants with cyanosis and irregular respirations symptoms considered characteristic of status thymicolymphaticus also displayed symptoms of

transparent and of delicate texture the hair is soft and fine Frequently the tonsils and adenoids are hypertrophied the palatal arch is high and the cervical glands are enlarged Schridde believes that enlargement of the lymphoid follicles at the base of the tongue is a constant finding though present also in other conditions The adult has the same general characteristics In the male the habitus resembles that of the female The body is finely proportioned and gracefully curved with slender waist large hips arching thighs and well molded arms Soft delicate almost hairless skin overlies a more than male panniculus The pubic hair does not grow up toward the umbilicus, but ends in a sharp, transverse line above the pubis transverse crines as in the female The penis often is small the glans pointed or arrowshaped The beard is thin and soft In the female the condition is less readily recognized, but is suggested when the lines of the body are unusually graceful the skin is extraordinarily delicate often velvety to the touch and hairless except for a scanty growth on small axillary pads and the mons veneris Since the condition is not static two types of the affection are encountered the status lymphaticus proper and recessive status lymphaticus (Symmers) The former *status lymphaticus proper* occurs during early life when the lymphoid tissues are naturally flourishing and is marked by notable changes in these tissues *Recessive status lymphaticus* is characterized by atrophic changes in the lymphoid structures varying in extent according to the time of involution No diagnostic test has yet been devised upon which the clinician may rely and he is forced to depend largely upon inspection At the Second International Pediatric Congress in 1930 there was general agreement only on the point that status lymphaticus exists The majority of pediatrists in this country attach much diagnostic importance to the presence of an enlarged thymus shadow in the roentgenogram although other symptoms of the status may be present when the thymus is small or absent when it is large

Clinical Associations — While clinical interest in the status lymphaticus always has centered in the fact that death may occur with startling rapidity and as the result of an apparently trivial occurrence it must be emphasized that not only is the condition compatible with a normal span of life but that a sudden termination happens but rarely

Lowered resistance to infections such as diphtheria typhoid fever influenza cerebrospinal meningitis and tuberculosis particularly of the bones joints and lymph nodes appears to be reflected in a higher death rate from these causes among persons presenting the features of a lymphatic constitution

Sudden death during the administration of an anesthetic or in the course of a minor operation expecially in children has led to special precautions being taken by many surgeons Roentgenograms of the chest are taken routinely in many children s hospitals an enlarged thymic shadow being considered as a

contraindication to an elective operation. A relative lymphocytosis which is a frequent feature of the status lymphaticus is thought by many to increase seriously the surgical risk and operation is avoided in such cases or is performed with increased caution. Administration of antitoxin, intravenous medication and the so-called shock therapy may result in sudden death when status lymphaticus is present.

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Cerebral hemorrhage occurring in young non-syphilitic subjects, while uncommon, is seen chiefly in those having a lymphatic constitution. The fatal rupture may occur as the result of a fall or of a blow which ordinarily would not cause serious injury. Such accidents are due to the hypoplasia of the small blood vessels of the brain found in this condition. This defect in the cerebral vascular system is believed by Symmers[4] to account for the fact that the five deaths from caisson disease recorded at Bellevue Hospital all occurred in men of this constitution.

Cause of Death. — That cardiac arrest is the immediate cause of death in status lymphaticus has long been known. How this is induced, however, is obscure. The early theory that pressure of an enlarged thymus upon the trachea, blood vessels and nerve trunks is responsible has been disputed. In its favor are cited the frequent finding in infants subject to attacks of laryngeal spasm of an enlarged thymus shadow on x-ray examination, the observation of Jackson[7] and others through direct bronchoscopic examination of tracheal compression by an enlarged thymus and occasional postmortem evidence of tracheostenosis. On the other hand elaborate studies by von Sury[8], Tamassia, Schoeppler[9] and others have shown that a degree of tracheal compression necessary to cause death could not have been exerted by the largest thymus removed at autopsy. Even thymic pressure as the cause of laryngeal stridor has been questioned increasingly. The relief produced in infants suffering from these attacks by irradiation which formerly was attributed to reduction of the size of the thymus through the destructive effects of the x-rays often appears too rapidly to be thus explained. It may be due to other effects of the roentgen rays. In this connection a recent report by Nesbit[10] is of interest. He noted that 28 infants with cyanosis and irregular respirations, symptoms considered characteristic of status thymicolymphaticus, also displayed symptoms of

transparent and of delicate texture the hair is soft and fine Frequently the tonsils and adenoids are hypertrophied, the palatal arch is high and the cervical glands are enlarged Schridde believes that enlargement of the lymphoid follicles at the base of the tongue is a constant finding though present also in other conditions The adult has the same general characteristics In the male the habitus resembles that of the female The body is finely proportioned and gracefully curved with slender waist large hips arching thighs and well molded arms Soft delicate almost hairless skin overlies a more than male panniculus The pubic hair does not grow up toward the umbilicus but ends in a sharp transverse line above the pubis transverse crines as in the female The penis often is small the glans pointed or arrowshaped The beard is thin and soft In the female the condition is less readily recognized, but is suggested when the lines of the body are unusually graceful the skin is extraordinarily delicate often velvety to the touch and hairless except for a scanty growth on small axillary pads and the mons veneris Since the condition is not static two types of the affection are encountered the status lymphaticus proper and recessive status lymphaticus (Symmers) The former, *status lymphaticus proper* occurs during early life when the lymphoid tissues are naturally flourishing and is marked by notable changes in these tissues *Recessive status lymphaticus* is characterized by atrophic changes in the lymphoid structures varying in extent according to the time of involution No diagnostic test has yet been devised upon which the clinician may rely and he is forced to depend largely upon inspection At the Second International Pediatric Congress in 1930 there was general agreement only on the point that status lymphaticus exists The majority of pediatrists in this country attach much diagnostic importance to the presence of an enlarged thymus shadow in the roentgenogram although other symptoms of the status may be present when the thymus is small or absent when it is large

Clinical Associations — While clinical interest in the status lymphaticus always has centered in the fact that death may occur with startling rapidity and as the result of an apparently trivial occurrence it must be emphasized that not only is the condition compatible with a normal span of life but that a sudden termination happens but rarely

Lowered resistance to infections such as diphtheria typhoid fever influenza cerebrospinal meningitis and tuberculosis particularly of the bones joints and lymph nodes appears to be reflected in a higher death rate from these causes among persons presenting the features of a lymphatic constitution

Sudden death during the administration of an anesthetic or in the course of a minor operation expecially in children has led to special precautions being taken by many surgeons Roentgenograms of the chest are taken routinely in many children s hospitals an enlarged thymic shadow being considered as a

Other Diseases

Graves disease often is associated with an enlarged thymus with or without other features of the status lymphaticus Thymic hypertrophy in these cases is believed to increase the danger of death with or without surgical intervention In a case of exophthalmic goiter recently seen by one of us in whom death had occurred suddenly the outstanding autopsy finding was an enormously enlarged thymus While the connection is not clear the frequent association suggests that some relationship exists

In Addison s disease thymic hyperplasia is a frequent finding A relationship between the thymus and the adrenals is suggested by the experimental work on animals of several investigators and this association is added evidence that the suprarenal bodies are in some way linked to the thymus[6]

In Hodgkin s disease the thymus often is greatly enlarged This probably is due to its involvement in the general lymphoid hyperplasia characteristic of that condition Thymic hypertrophy has been reported also in certain cases of leukemia[68] and of hemophilia[69]

Primary Tumors of the Thymus

Thymoma was the term suggested by Grandhomme[70] in 1900 for the most frequently occurring tumor of the thymus Though widely used the term has had a varied significance Bell[67] applied it to non malignant growths only Margolis[71] to all tumors of parenchymal origin Recently it has been suggested that the term be used for all malignant thymic tumors while Symmers[72] believes that the practice of naming tumors after the organs in which they arise is a philologic desecration and would drop the term altogether

Benign tumors of the thymus have been described chiefly in cases of myasthenia gravis In a recent review of 67 cases of myasthenia with complete autopsy findings Lievre[63] noted that in 23 similar clearly limited encapsulated easily isolated lympho-epithelial tumors were described Bell[67] and others have considered these growths to be benign tumors Ewing[73] is of the opinion that non malignant thymic growths (lymphadenomas) represent various degrees of hyperplasia and this view is shared by Norris[64] and others Marked hyperplasia is noted frequently in aberrant thymus tissue and may resemble neoplasm

Malignant thymic tumors are probably less rare than is suggested by the number of reported cases (217 to August 1936) and should be watched for carefully since early diagnosis is essential Symmers[66] found 25 malignant thymic tumors in 17 000 autopsies at Bellevue Hospital while at the University of Pittsburgh two cases occurred in 3725 autopsies[74] At the Protestant Epis

vagitonia and tetany Of the 28 only 12 were reported by the roentgenologist as having a substernal shadow of sufficient width for a diagnosis of thymic enlargement Some were given radiation over the thymus, while to the others calcium was administered intravenously In all cases the symptoms were relieved equally As the calcium content of the spinal fluid, which previously had been deficient increased after both types of therapy it was concluded that the symptoms had resulted from lack of calcium rather than from thymic enlargement

Symmers has advanced the view that sudden death in cases of status lymphaticus is due to anaphylaxis resulting from sensitization and shock from liberation of nucleoprotein from necrotic germinal centers Others have assumed that increased vagal tone combined with a weakness of the sympathetic system brings about the sudden cardiac standstill Lowered general resistance and hypersusceptibility to shock induced by chemical and physical agents are characteristics of Addison s disease, exophthalmic goiter and other conditions involving the endocrine organs as well as of status lymphaticus and further knowledge concerning the complex interactions of the glands of internal secretion is necessary before these and many other questions can be answered

Myasthenia Gravis

Thymic enlargement due to hyperplasia or neoplastic growth has been noted frequently in cases of myasthenia gravis since the association was first reported by Weigert[61] in 1901 It was present in 27 (about 50 per cent) of 56 autopsied cases collected by Bell[62] in 1917 in 56 (83 per cent) of 67 cases discussed by Lievre[63] and in 2 (50 per cent) of 4 cases reported by Norris[64] in 1936 In 250 cases reviewed by Starr[65] in 1912 in many of which before 1901 the thymus probably had not been investigated carefully the incidence was 28 per cent and Symmers gave the conservative estimate of 20 per cent in 1932[66] Many authors have attempted to explain the myasthenia on the basis of the thymic abnormality It was first suggested that the condition might be produced by metastases from a malignant thymic tumor and later that it might be due to excessive secretion by the thymus The absence of demonstrable pathological changes in the thymus in at least half the cases the failure to produce the clinical picture of myasthenia by experimental administration of potent thymus extracts and finally the symptomatic control of the condition by the administration of glycine and prostigmine militate against these points of view At present it seems best to regard myasthenia gravis as a disturbance of the neuromuscular mechanism possibly on an endocrine basis[64] in which case the thymus may play a rôle It is also possible that the hyperplasia and tumor formation may be secondary to the factors causing the condition

bryonal thymus found most frequently in syphilitic infants Funke was able to demonstrate lymphoid tissue and Hassall's corpuscles in the walls of a cyst embedded in the thyroid Similar cysts lined by columnar epithelium have been found in cases of exophthalmic goiter (2) cysts produced by degeneration of lymphocytes which have invaded Hassall's corpuscles The abscesses described by Dubois[76] were shown by Chiari[77] to consist of corpuscles distended by lymphocytes and are of this type (3) dermoid cysts which may arise from the branchial clefts or ventral ectoderm have been found but are rare

Therapeutic Uses of Thymus Extracts

Extracts of the thymus have been employed chiefly for the promotion of growth and development Until recently the preparations have been too variable and inactive for conclusions to be drawn from the results obtained Rowntree and his coworkers[8] have been administering their potent extract to an appreciable number of cases of retarded children during the past year While too little time has elapsed for definite results to be determined they are said to be encouraging especially in the very young cases Thymus extract (Hanson) recently has been employed in treatment of osteogenesis imperfecta tarda[79] and other extracts[80] have been used in cases of defective or abnormal skeletal development

BIBLIOGRAPHY

1 STARLING Principle of Human Physiology p 964 5th ed Lea & Febiger Philadelphia 1930
2 FRIEDLEBEN A Die Physiologie der Thymusdruse in Gesundheit und Krankheit vom Standpunkte experimenteller Forschung und klinischer Erfahrung ein Beitrag zur Lebensgeschichte der Kindheit Frankfurt a M Literarische Anstalt 1858
3 BASCH K Monatschr f Kinderh 1908 VII 541
4 SOLI U Arch Ital de Biol 1909 LII 217
5 NITSCHKE A Ztschr f d ges exper Med 19 9 LXV 637
6 KLOSE HEINRICH Arch f klin Chir 1910 XCII 1125
KLOSE HEINRICH and VOGT HEINRICH Beitr z klin Chir 1910 LXIX 1
7 PARK E A and McCLURE R D Am Jour Dis Child 1919 XVIII 31
8 MARINE DAVID and MANLEY O T Jour Lab and Clin Med 1917 18 III 48
9 SOLI U quoted by Rowntree and others Ann Int Med 1935 IX 360
10 ANDERSEN D H Jour Physiol 1932 LXXIV 63
11 EINHORN N H and ROWNTREE L G Endocrinology 1936 XX 342

copal Hospital in Philadelphia three proven cases have been admitted during the past two years. Classification of the type of tumor is difficult, and until the origins of the thymic cells are determined none can be considered final. The 25 cases in the Bellevue Hospital series were classified as follows: 8 peritheliomas from the connective tissue of the walls of small blood vessels, 9 lymphosarcomas from the lymphocytic elements, 5 Hodgkin's "sarcomas", 2 epitheliomas from the reticulum cells and 1 spindle cell sarcoma from the connective tissue framework. All malignant thymic tumors have a similarity in gross appearance though they differ microscopically. They are located in the anterior mediastinum and tend to be encapsulated in it. The more rapidly growing tumors are soft and vascular but the majority are firm due to fibrosis and occasionally contain areas of necrotic softening or cysts. They vary in color from a lemon yellow to a grey, milky brown or salmon. There is no true capsule, but most tumors compress rather than invade the trachea, bronchi, great vessels, lungs and heart. Not infrequently, however, they may be adherent to adjacent tissues having broken through their pseudocapsule and invaded the pleura, pericardium or trachea by extension rather than by metastasis. In the more malignant cases metastasis to a distant organ may occur. Many tumors of the thymus resemble lymphosarcomas. They are composed histologically of a diffuse growth of round polyhedral and giant cells with a variable amount of connective tissue stroma and blood vessels replacing the normal glandular structure. Lymphocytes are present in great numbers though reticulum cells probably are predominant. Other tumors resemble carcinomas, being composed chiefly of pavement, cuboidal, or rarely columnar epithelium with or without Hassall's corpuscles and comparatively few lymphocytes. Some growths appear to spring from the connective tissue stroma. Ewing[73] points out that practically all reports of carcinomas of the thymus have come from French authors, while tumors often having similar histologic characters have been called sarcomas in the German literature. He maintains that the majority of thymic tumors arise on the basis of an infectious granuloma, thus offering a relatively simple explanation for the great variety of structural forms represented. From the practical clinical standpoint differentiation is chiefly important since tumors resembling lymphosarcomas or Hodgkin's "sarcomas" are radiosensitive, while other thymic tumors are but little if at all affected by the x-ray or by radium. However, the ultimate prognosis is bad in both types. During the past year death occurred in two patients observed by us within a few months, although in each case the mediastinal shadow had been reduced by x-ray treatments to a small portion of its former size.

Thymic cysts are met with occasionally. These are of several types occurring in the gland proper or in aberrant thymic tissue in the mediastinum or cervical region: (1) cysts formed from persistent epithelial canals of the em

47 JEANDFLIZE P LUCIEN M and LARIOSOT J Compt rend Soc de Biol 1909 LXVI 942
48 ROWNTREE L G CLARK J H STEINBERG A and HANSON A M Jour Am Med Assoc 1936 CVI 370
49 WASSON W W Arch Otolaryng 1926 IV 405
50 BOYD EDITH Am Jour Dis Child, 1924 XXXIII 867
51 FLATER FELIX quoted by MARINE DAVID Arch Path and Lab Med 1928 V, 661
52 KOPP, J Denkwürdigkeiten in der arztlichen Praxis Vol V Frankfurt a M 1830
53 PALTAUF A Wien klin Wchnschr 1889 II 877 and 1890 III 172
54 SYMMERS DOUGLAS Am Jour Surg 1934 XXVI 7
55 ESCHERICH K Berl Klin Wchnschr 1896 XXXIII 645
56 Cited by SYMMERS DOUGLASS Am Jour Surg 1934 XXVI 12
57 JACKSON C Jour Am Med Assoc 1907 XLVIII 1753
58 VON SURY K Vrtljschr f gerichtl Med 1908 XXXVI 88
59 SCHOEPPLER H Centralb f allg Pathol u path Anat 1914 XXV 289
60 NESBIT HAROLD T Arch Ped 1934 LI 55
61 WEIGERT CARL Gesammelte Abhandlungen First Edition p 581 Berlin 1906 and Pathologisch anatomischer Beitrag zur Erbschen Krankheit (Myasthenia Gravis) 1901
62 BELL E T Jour Nerv and Mental Dis 1917 XLV 130
63 LIÈVRE J A Presse Méd 1936 XLIV 991
64 NORRIS E H Am Jour Cancer 1936 XXVII 421
65 Quoted by NORRIS Am Jour Cancer 1936 XXVII 421
66 SYMMERS DOUGLAS Ann Surg 1932 XCV 572
67 MARINE DAVID Arch Path and Lab Med 1928 V 661
68 FABIAN ERICH Centrbl f allg Path u pathol Anat 1908 XIX 650
COENEN HERMANN Arch f klin Chir 1904 LXXIII 443
MARCHEL G BRUN C and GRUPFER Bull et Mém Soc Méd d Hôp de Paris 1034 L 1715
69 ACLAND THEODORE D Tran Path Soc London 1885 XXXVI 401
70 GRANDHOMME F Uber Tumorem des vorderen Mediastinum und ihre Baziehungen zu der Thymusdruse Inaugural Dissertation Heidelberg 1900
71 MARGOLIS H M Am Jour Cancer 1931 XV 2106
72 SYMMERS DOUGLAS Ann Surg 1932 XCV 545
73 EWING JAMES Neoplastic Disease p 968 3rd ed 1928
74 DECKER H R Jour Thor Surg 1935 IV 445
75 FUNKE N S Phila Path Soc 1908 XI 59
76 DUBOIS P Gaz med Paris 1850 V 392
77 CHIARI H Ztschr f Heilk 1894 XV 403
78 ROWNTREE L G Personal communication
79 SECORD E W WILDER R M and HENDERSON M Proc Staff Meet Mayo Clin 1936 XI 1
80 MARX J Centrbl f Chir 1936 LIII 208

12 GUDERNATSCH, J F Am Jour Anat 1913-14 XV 431
13 UHLENHUTH EDUARD Jour Exper Zool, 1918 XXV, 135
14 GROEBBELS F Zeit Biol 1923 LXXVII 249
15 SWINGLE, W W Biol Bull Marine Biol Lab 1917, XXXIII 116
16 HEWER EVELYN E Jour Physiol 1914 XLVII, 479, and 1916 L 434
17 HOSKINS F R Endocrinology 1918 II 241
18 RIDDLE OSCAR Am Jour Physiol 1925 LXXI 413
19 RIDDLE OSCAR and KRIZENECKY, JAROSLAV Am Jour Physiol 1931 XCVII 343
20 GREENWOOD ALAN W Proc Soc Exper Biol and Med 1931 32 XXIX 38
21 GROEBBELS F Pfluger s Arch 1934 CCXXXV 26
22 SCHAZILLO B A Archiv exper Zellforsch 1925 I 160
23 MENDELEEFF P Deutsch med Woch 1934 XXXIX 1628
24 NITSCHKE A Mon chr f Kinderhlk 1928 XLI 128 Zeit f exper Med 1929 LXV 637 651
25 NITSCHKE A Klin Woch 1929 VIII 1
26 ASHER DORIS Biochem Zeit 1933 CCLVII 209
27 NOWINSKI W W Biochem Zeit 1930 CCXXVI 415
28 NOWINSKI W W Biochem Zeit 1932 CCXLIX 4 1
29 BACHMANN H Biochem Zeit 1934 CCLXVIII 272
30 HAMMAR J AUG Die normal morphologische Thymusforschung im letzten Vierteljahrhundert Analyse und Synthese neb t einigen Worten zu der Funktionsfrage p 3,4 Leipzig 1936
31 ROWNTREE L G CLARK J H and HANSON A M Jour Am Med Assoc 1934 CIII 142,
ROWNTREE L G CLARK J H STEINBERG A HANSON A M EINHORN N H and SHANNON W A Ann Int Med 1935 IX 350
32 ROWNTREE L G Personal communication
33 PARHON C J CAHANE M and MARZA V Compt rend Soc de Biol 1926 XCV 795 1927 XCVI 1177 and 1927 XCVII 1027
34 SECKEL H Z Kinderhlk 1927 XLIV 437
35 ROBOZ P Ergebn d inn Med 1935 XLVIII 470
36 VON KOSTYÁL L An Kinderhlk 1935 CV 20
37 EINHORN N H and ROWNTREE L G Science 1936 LXXXIII 23
38 CRAMER W DREW A H and MOTTRAM J C Lancet 19 1 II 1202
39 CALZOLARI A Arch Ital de Biol 1898 XXX 74
40 HENDERSON J Jour Physiol 1904 XXXI 222
41 GOODALL A Jour Physiol 1905 XXXII 191
42 GELLIN O Zeit f exper Path u Therap 1911 VIII 71
43 PATON D NOEL Jour Physiol 1905 XXXII 28
44 MARINE DAVID MANLEY O T and BAUMANN EMIL J 1924 XL 429
45 JAFFÉ H L Jour Exper Med 1924 XL 323
46 SCOTT and BRADFORD quoted by Ludovico La Grutta Riv pat per 1933 X 297

CHAPTER III

DISEASES OF THE SPLEEN

HERBERT Z GIFFIN

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DISEASES OF THE SPLEEN

HERBERT Z. GIFFIN

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Introduction and Historical Note

In a chapter of this scope it is impossible to discuss subjects in detail, nor can the literature be analyzed. Frequently, contrary to the natural inclination of the author, statements that are more or less dogmatic must be made. In fact, the discussion evolves as a framework on which a study of the literature can be elaborated. Any intrinsic value that my notes may have is the result of my interest in clinical hematology and diseases associated with splenomegaly that has existed for more than twenty years, and especially of the opportunity

I have had to study cases in a large clinic I have had no experience in experimental work

The history of investigation on the spleen might be divided into three eras that of the ancients which might be termed the era of mysticism an era extending well into the nineteenth century the period of transition and skepticism and the modern era of empiric inquiry and physiologic investigation The Greek and Roman physicians and philosophers recognized that the spleen was not necessary to life but held many sophic and fantastic views with regard to this organ The teachings of Galen who associated the spleen with black bile and melancholy held sway until the sixteenth century and even today the remnants of this idea are present in our language Anatomic knowledge began to accumulate with the observations of Malpighi in the seventeenth century but progress was slow and the era of skepticism is exemplified by the story of the professor in physiology who year after year stated Gentlemen we now come to the spleen concerning the spleen we know nothing that is all regarding the spleen

The era of fundamental investigation was inaugurated by the development of histology and empiric observation of animals which had been subjected to splenectomy Later observations on the results of splenectomy in man further stimulated an interest which has led to the demonstration of many anatomic and physiologic facts especially with respect to the structure of the spleen the spleen as an organ of the hematopoietic and reticulo-endothelial systems and the relation of the spleen to the portal system So many interesting discussions on the history of investigation on the spleen and on splenectomy can be found in the textbooks and reviews reference to which will be given in the bibliography that I shall proceed directly to a consideration of the present status of our knowledge of the fundamentals

ANATOMY AND HISTOLOGY *

The spleen is a lymphoid organ without lymphatic channels it is the largest lymphoid organ of man It contains no epithelium and has no duct The normal spleen is soft friable vascular and lies well protected by ribs high under the diaphragm in the left hypochondrium posterior to the fundus of the stomach The normal spleen weighs approximately 180 gm and its length is about 12 cm considerable variation in size occurs a very small spleen is not infrequently seen especially in older persons and even absence of the spleen is well authenticated The spleen is essentially a lobated and lobulated organ Lobated spleens are occasionally seen in man and are common in some of the

* I wish to acknowledge the assistance of Charles H Watkins in the arrangement of data on anatomy histology and embryology

lower animals The spleen has three distinct surfaces, phrenic, gastric and renal In the gastric surface is found the hilum a fissure about 4 cm in length into which the nerves and blood vessels pass The nerves consist of non medullated fibers derived from the celiac plexus and they follow the vessels

In the hope of fostering clarity the anatomy and histology of the spleen may be considered under three headings (1) the framework of the spleen, (2) the splenic nodules and the splenic pulp and (3) the circulation of the spleen

The Framework of the Spleen — The spleen is covered by a serous coat contributed by the peritoneum and is also completely invested by a distinct capsule, or tunica albuginea composed of dense fibrous tissue numerous elastic fibers and in the deeper layers sparse bundles of involuntary muscle The fibrous capsule enters the organ at the hilum, supporting the blood vessels and nerves The capsule and the larger trabeculæ contain the only demonstrable lymph channels of the spleen Numerous trabeculæ extend from the capsule pass into the substance of the gland and break up into numerous fine processes which form the supporting framework The arrangement of this framework results in the formation of fairly regular compartments the so-called splenic lobules According to Mall each lobule is bound by three interlobular trabeculæ, from which secondary intralobular processes penetrate into the lobule and by which each typical lobule is divided into ten primary compartments The trabeculæ themselves are not isolated but freely communicate with the intervening trabeculæ and form only incomplete partitions The splenic lobules anastomose in all directions The finer framework of the spleen consists of reticular cells and fibers very delicately arranged in basket fashion The reticular fibers also encircle the veins and are present in the malpighian corpuscles Small reticular cells are found throughout the pulp and along the arteries, where they form a definite sheath on the outside of the vascular wall, the so-called perithelium These reticular cells or so called reticulo endothelial cells, are by no means peculiar to the spleen They are similar to and potentially identical with the clasmatocytes of Ranvier the histiocytes of Aschoff and Kiyono Mallory s endothelial leukocytes the Kupffer cells of the liver, and the ' resting wandering cells ' of Maximow they may also be related to the monocytes of the circulating blood These cells may become actively phagocytic and have much to do with the destruction of bacteria and the elimination of pigment and obsolescent or fragmented erythrocytes

The Splenic Nodules and the Splenic Pulp — The splenic nodules are small masses in the spleen composed of lymphocytes At the point where the artery leaves the trabecula and passes into the lobule the adventitia of the intralobular artery becomes infiltrated with lymphocytes forming a lymphoid mass which surrounds not only the artery of the lobule but its many branches The relation of the arteries and veins to this lymphoid tissue is the same as in lymph

nodes elsewhere in the body except for one fundamental difference the splenic lobule contains no lymphatic channels Large lymphocytes similar to the cells of the germinal centers of lymph nodes are present in the central portions of the splenic nodules There is some question as to whether these lymphatic masses should be regarded as independent tissue or as an intimate part of the splenic pulp

The splenic pulp fills the spaces within the reticular framework and constitutes the largest part of the bulk of the organ The tissue which occupies the compartments is arranged as anastomosing cylindric masses the so-called pulp cord which might be said to resemble crudely irregular cucumbers Normally all the various types of cells present in the general circulation are found in the splenic pulp and in addition nongranular phagocytic reticular cells called splenocytes and macrophages are found An occasional myelocyte may be seen but nucleated erythrocytes are rarely present

The Circulation — The splenic artery and the splenic vein are very large and the vein shows a remarkable contractility on electric stimulation The splenic artery usually branches at the hilum but occasionally it breaks up into branches before reaching the hilum The branches of the splenic artery within the spleen are numerous and tortuous and run for variable distances in the trabeculae breaking up into smaller vessels Each of these smaller vessels enters the proximal end of the apex of a splenic lobule through the middle of which it passes giving off lateral twigs one for each compartment of the lobule The artery of the compartment gives off branches which are called the terminal arterioles or penicillary arteries The terminal arterioles within the pulp cords expand near their extreme end into the so-called ellipsoids or ampullae of Thoma which are lined by endothelium Mall divided the ampulla of the terminal arteriole into three portions (1) a definite dilatation lined by spindle cells which are directly continuous with the endothelial cells of the arteriole (2) a portion less dilated containing many openings and (3) a portion in which the walls again become compact By means of injections it has been shown that the walls of the middle portion of the ampulla are more permeable than those of the first and third portions There is some evidence that the ampulla exerts a valve like action and prevents reflux of blood Beyond the distal end of the ampulla there are dilated vascular spaces known as venous sinuses The walls of the venous sinuses possess a peculiar structure the function of which is not that of endothelium The walls of the venous sinuses are lined by long narrow cells which run parallel to the long axis of the vessel and lie somewhat apart permitting of slit like spaces between them The bodies of these cells protrude into the lumens of the sinuses the cells themselves are actively phagocytic have the typical structure of reticular cells and are identical with the reticular cells of the pulp and with those of other portions of the spleen The venous sinuses empty into the veins which lie at the periphery of the splenic lobules

The type of circulation between the terminal arteriole and the vein has been the subject of much discussion, and the question still is undecided Weidenreich and others held the theory that there was a closed system of capillaries and venous sinuses and believed that the migration of cells was by diapedesis Mall was not able to obtain satisfactory evidence in favor of this view Others claim that there is more evidence for an entirely open circulation they believe that the blood which leaves the arteriole and the ampulla passes into the meshes of the network of reticulum, and thence into the venous sinuses and veins The histologic structure, as it is now understood, seems to be compatible with a partially open and a partially closed system Under certain conditions most of the blood may pass directly from the terminal arteriole and ampulla to the venous sinuses and veins under other conditions, such as rhythmic contraction of the spleen the blood cells may circulate through the reticulum of the pulp by way of the porous portions of the ampullæ and the walls of the venous sinuses, thence into the veins

Embryology

Although the details of the development of the spleen are not well known it is established that the spleen appears in the fifth embryonic week as a thickening of the mesoderm of the dorsal mesogastrium It consists of a mass of mesenchymal cells and increases in size by hyperplasia of mesenchymal elements Some observers believe that the spleen receives cells from the mesothelium of the body cavity in addition to cells from the primary mesenchymal tissue Laguesse Tonkoff Thiel and Downey have shown that after a pig embryo has reached the length of 15 mm the spleen does not receive cells from the mesothelium As cytogenesis of the mesenchymal cells progresses there is differentiation into two general types of cells Some of the cells remain connected in a syncytium and later assume a star shaped form These constitute the reticular framework of the spleen Other mesenchymal cells lose their connections with the surrounding syncytium and become free cells situated in the meshes of the framework later on by mitosis they give origin to erythrocytes granular leukocytes lymphocytes and megakaryocytes In the higher vertebrates the myeloid function of the spleen ceases at about the time of birth although the formation of lymphocytes persists throughout life

Danchakoff found that in the normal development of the spleen of the chick the earliest vascular elements are exclusively venous Sinuses appear in the mensenchyme and later connect with the primitive veins These sinuses join, forming a network which provides the spleen with a spongy structure Secondarily arteries and their branches grow into the spleen from without ramify by budding and finally unite with the preformed sinuses Sabin demon

strated that in a pig embryo 3 cm long both arterial and venous capillaries were present Thiel and Downey by a study of serial sections of pig embryos found that in embryos under 6 cm in length the only vascular elements are narrow irregularly branching capillaries which present a distinct endothelial lining They found no instances of large tissue clefts or sinuses during the first five weeks of embryonic life When an embryo reaches 4 to 6 cm in length, clear and somewhat open areas appear in the mesenchymal tissue in which distinct slits later become evident In the margins of the slits the mesenchymal cells still retain their irregular processes The cells bordering the sinuses sever their connections with the mesoderm some of them become rounded and basophilic and lie within the sinuses forming large lymphocytes Thiel and Downey stated that the mesenchyme bordering the primitive sinus is very active in this process forming free cells in the sinuses which later function as the parent cells of the erythroblasts that differentiate within the sinuses In embryos 6 to 7 cm long connection is established between the primitive splenic sinuses and the capillary bed as is indicated by the appearance of fully differentiated erythrocytes within the sinuses Thiel and Downey stated that the wall of the sinus is composed of a close network of reticulum, which is a continuation of that of the surrounding pulp This study led to the conclusion that the sinuses are never lined with endothelium but are merely irregular channels through the reticulum in the adult as well as in the embryo Cells from the pulp can enter the sinuses readily through the normal openings which occur in the reticular wall Sabin and her coworkers have expressed the belief that the sinuses are lined with true endothelium as a result of the development of the sinuses from the capillary bed whereas the work of Thiel and Downey seems to demonstrate that the sinuses are lined by reticulum and that the sinuses and capillaries develop independently and later unite

Physiology

The physiology of the spleen can be considered under the following heads (1) blood production (2) blood destruction (3) possible inhibitory and stimulating effect of the spleen on the hematopoietic system (4) contractility and function as a reservoir (5) circulatory relationships (6) function of filtration (7) relationship to immunity (8) relation to metabolism (9) experimental splenectomy and (10) physiologic effect of splenectomy on man

Blood Production — During the latter part of the embryonic and throughout the fetal period the spleen takes an active part in the formation of all types of blood cells At approximately the time of birth this function is assumed by the bone marrow although lymphocytes and perhaps other types of cells notably monocytes are produced by the spleen throughout life The spleen however

The type of circulation between the terminal arteriole and the vein has been the subject of much discussion, and the question still is undecided Weidenreich and others held the theory that there was a closed system of capillaries and venous sinuses and believed that the migration of cells was by diapedesis Mall was not able to obtain satisfactory evidence in favor of this view Others claim that there is more evidence for an entirely open circulation they believe that the blood which leaves the arteriole and the ampulla passes into the meshes of the network of reticulum, and thence into the venous sinuses and veins The histologic structure, as it is now understood, seems to be compatible with a partially open and a partially closed system Under certain conditions most of the blood may pass directly from the terminal arteriole and ampulla to the venous sinuses and veins, under other conditions, such as rhythmic contraction of the spleen the blood cells may circulate through the reticulum of the pulp, by way of the porous portions of the ampullæ and the walls of the venous sinuses, thence into the veins

Embryology

Although the details of the development of the spleen are not well known, it is established that the spleen appears in the fifth embryonic week as a thickening of the mesoderm of the dorsal mesogastrium It consists of a mass of mesenchymal cells and increases in size by hyperplasia of mesenchymal elements Some observers believe that the spleen receives cells from the mesothelium of the body cavity in addition to cells from the primary mesenchymal tissue Laguesse Tonkoff Thiel and Downey have shown that, after a pig embryo has reached the length of 15 mm the spleen does not receive cells from the mesothelium As cytogenesis of the mesenchymal cells progresses there is differentiation into two general types of cells Some of the cells remain connected in a syncytium and later assume a star shaped form These constitute the reticular framework of the spleen Other mesenchymal cells lose their connections with the surrounding syncytium and become free cells situated in the meshes of the framework later on by mitosis they give origin to erythrocytes granular leukocytes lymphocytes and megakaryocytes In the higher vertebrates the myeloid function of the spleen ceases at about the time of birth although the formation of lymphocytes persists throughout life

Danchakoff found that in the normal development of the spleen of the chick the earliest vascular elements are exclusively venous Sinuses appear in the mensenchyme and later connect with the primitive veins These sinuses join forming a network which provides the spleen with a spongy structure Secondarily arteries and their branches grow into the spleen from without ramify by budding and finally unite with the preformed sinuses Sabin demon

most important factor in blood destruction and that these fragments are phagocytosed and converted by the endothelial phagocytes of the tissues. As would be expected after the spleen is removed the other hematopoietic tissues containing the reticulo-endothelial cells rapidly compensate for loss of the spleen. There are certain diseases in which destruction of erythrocytes predominates very strikingly in the spleen. The fact that in hemolytic icterus after splenectomy there is marked reduction in the amount of blood destruction indicates that at least in this disease there is hyperactivity of blood destruction in the spleen. From the excellent results obtained by splenectomy in essential thrombocytopenic purpura one would infer that the spleen has an important relation to the maintenance of the number of blood platelets. The rise in the number of blood platelets which occurs after removal of even the normal spleen suggests that destruction of platelets may be a normal function of the spleen and that this function may be hyperactive in hemorrhagic purpura. On the other hand, so far platelet counts of the blood from the splenic artery and splenic vein have not shown definite variation in the platelets, and the theory has also been advanced that the spleen has an inhibitory effect on formation of platelets. However, the rapid rise in the platelet count after splenectomy seems to indicate a more direct effect exerted by the spleen. If there is hyperactivity of destruction of platelets in the spleen in hemorrhagic purpura, the postoperative course of patients with this disease would seem to indicate that other portions of the hematopoietic system do not, to any appreciable degree, take over this malfunction.

There are three theories concerning the destruction of erythrocytes which furnish evidence of the relative activity of the various organs. Histologic studies indicate that the spleen is more active in actual destruction of erythrocytes than is the bone marrow or liver. Studies on the deposition of iron indicate greatest accumulation in the liver. Experimental studies by Mann and Bollman give evidence of greater production of bilirubin by the bone marrow than by liver or spleen. Although it cannot be concluded definitely that the spleen is the most active site of destruction of erythrocytes, this conception is corroborated by the improvement in anemia which follows removal of the spleen in man for various conditions. The conversion of the products of destruction of erythrocytes may be more active in the bone marrow and liver, phagocytosis more active in the spleen.

Possible Inhibitory and Stimulating Effect of the Spleen on the Hematopoietic System. —Normally there is a remarkable balance between the formation of blood and its destruction in order to preserve constancy in the number of blood cells. The fact that no appreciable difference could be found between arterial and venous blood of the spleen led Krumbhaar and Musser to conclude that experimental postsplenectomy anemia of dogs is best explained by the loss of some

retains its potential function of producing erythrocytes and granular leukocytes for in severe anemia and in leukemia and in other pathologic conditions in which there is an excessive demand for erythrocytes erythropoietic tissue can be found scattered throughout the splenic pulp and in leukemia and in some very severe forms of anemia myeloid metaplasia can be observed In childhood the production of lymphocytes doubtless is very active and accounts in part for the lymphocytosis in the blood of children In the adult an increased number of lymphocytes has been found in the blood following contraction of the spleen, experimentally produced, either by electric current or by epinephrine It is certain therefore that there is active production of lymphocytes by the spleen in adult life

The lymphocytes which are produced by the spleen enter the circulation either directly through the splenic sinuses or by diapedesis, rather than through lymphatic channels as is the case in lymph nodes Comparative blood counts of the arterial and venous blood of the spleen have been made by Krumbhaar and others but appreciable difference has not been demonstrated, and there is little evidence that the spleen has an important part in formation of erythrocytes normally in the adult The evidence, which favors the belief that monocytes are produced in the spleen of the adult, is indirect and rests largely on the fact that it has been demonstrated that monocytes are derived in part from reticulo endothelial cells and that monocytes have not been demonstrated in smears made of the lymph from the thoracic ducts of animals This absence of monocytes in the lymph precludes the probability that they are formed in the lymph nodes of the abdominal cavity

Blood Destruction — Rous concluded that phagocytosis and fragmentation are the two methods by which erythrocytes normally are destroyed In pathologic conditions the erythrocytes may be destroyed also by means of hemolysis and may be rendered more susceptible to destruction by means of agglutination or because of fundamental changes in the erythrocytes themselves The reticulo endothelial cells of the spleen have the important function of phagocytosis chiefly of phagocytosis of fragmented erythrocytes but also of other abnormal erythrocytes and possibly occasionally of normal erythrocytes This action of the reticulo-endothelial cells is not confined to the spleen, however, but according to Aschoff Kiyono and others cells elsewhere have a similar function and possibly a similar origin namely the Kupffer cells of the liver the wandering cells of the connective tissue the large mononuclear cells, the monocytes of the blood and the large phagocytic cells of the spleen, bone marrow and lymph nodes It is also from reticulo-endothelial cells that the giant cells or epithelioid cells seen in tuberculosis the characteristic cells in Gaucher s disease and the Dorothy Reed cells in Hodgkin s disease are formed Sabin and Doan have confirmed Rous' contention that fragmentation of erythrocytes is the

Circulatory Relationships —The spleen is an intimate part of the portal system and its activity influences the amount of blood which passes through the liver It has been suspected in experimentation on animals that after removal of the spleen the volume of blood which passes through the liver is considerably reduced, possibly by [illegible]0 per cent W J Mayo for many years has been an exponent of the value of reducing the amount of blood passing through the liver by a splenectomy he advocated this procedure as a result of surgical experience With fibrosis of the spleen and other pathologic conditions normal contractions may be interfered with and chronic engorgement occur with gradual enlargement of all of the vessels associated with the spleen Most important from the standpoint of engorgement are the short gastric vessels and the veins of the cardiac orifice of the stomach because of the danger of gastro-intestinal hemorrhage

Function of Filtration — There has been a considerable amount of discussion of the spleen as a possible filter The histology of the spleen makes it theoretically possible for gross particles to pass through the porous portions of the ampullae and become lodged in the splenic pulp where eventually they either become destroyed by lysis and phagocytosis or remain as foreign deposits It is known that the blood may be freed of foreign particles by the spleen and that bacteria are taken up by the reticular cells It is probable however that there is little actual filtration in a mechanical sense aside from the factor of stasis and delay and that the same end is accomplished by phagocytosis of bacteria of foreign particles and of fragments of erythrocytes Chemotactic influences doubtless are active also Under some condition phagocytosis and filtration must be very much reduced in view of the fact that the spleen may become a nest of organisms or of plasmodia

Relationship to Immunity — Experimental evidence seems to indicate that the spleen plays a part in increasing the resistance to infections but it is also likely that in itself the spleen may be only temporarily effective and that whatever functions it may have in this respect are taken over by other tissues after splenectomy The literature on the relation of the spleen to immunity both in infection and tuberculosis is confusing and many reports have been published in recent years on the effect on immunity of blockade of the reticulo-endothelial system

Relation to Metabolism — Reticular cells throughout the body have the power to remove lipoids from the blood and both to convert them and store them This function is demonstrated in various pathologic conditions such as lipemia of diabetes Gaucher's disease Niemann's disease and Christian's syndrome Iron is accumulated and distributed by the tissues of the spleen Removal of the spleen is not followed by any definite disturbance of metabolism and it is not likely that the spleen takes a definite part in metabolism otherwise

substance contained within the spleen, which exerts a stimulating effect on the bone marrow and that this anemia is due to lack of formation of blood rather than to increase in its destruction. They also demonstrated that recovery from this anemia is more rapid with the administration of splenic extract, and that the anemia is only transitory and disappears as soon as compensatory hyperplasia of the bone marrow occurs. Others have suggested that the spleen produces an internal secretion synthesized from destroyed erythrocytes and that this secretion reduces the resistance of the erythrocytes and acts as a hormone which probably is modified by the liver and stimulates the erythropoietic activity of the bone marrow. In contradistinction to these views however, the usual occurrence of leukocytosis and thrombocytosis following splenectomy, both in the experimental animal and in man, seems to indicate that the spleen has an inhibitory action on hematopoiesis. Moreover, a definite increase in the volume of the bone marrow has been demonstrated experimentally following splenectomy. It would seem therefore that the evidence in favor of the spleen having an inhibitory effect on hematopoiesis outweighs the evidence for its having a stimulating effect. The balance between blood formation and blood destruction probably is determined not by the spleen only but by the various portions of the entire hematopoietic system and the changes which occur following splenectomy are modified as soon as there is compensation by the other hematopoietic organs.

Contractility and Function as a Reservoir.—The normal spleen undergoes rhythmic contractions and also becomes notably distended during the process of digestion. Smooth muscle tissue is found in the capsule and in the larger trabeculæ and vasomotor nerves are derived from the autonomic system. Stimulation of these nerves results in contraction of the spleen. Periodic contraction of the spleen probably is an important phenomenon from the circulatory standpoint and also assists in the extrusion of lymphocytes. It has been suggested that this probably accounts for the fact that metastatic involvement of the spleen in malignant tumors is uncommon on the basis that cells passing through the spleen do not easily find a resting place. The exact reason for dilatation of the spleen during digestion is not clear. It is probably due to generalized engorgement of the abdominal viscera. Harm probably results only when the spleen is unable to free itself of blood following digestion, as is the case in pathologic conditions associated with fibrosis.

Recent work of Barcroft and his associates indicates that the content of the spleen is more completely expelled into the circulation during exercise, and that under most normal conditions the spleen acts as a reservoir of erythrocytes. In emergency the content may be delivered to the organism. It acts as a balance on the circulation both with respect to volume of circulating blood and with respect to the number of erythrocytes.

Clinical study of cases leads to the following physiologic deductions (1) there is improvement of the anemia both of the secondary type and temporarily even of the primary type (2) there is great increase in the number of platelets and modification of the various factors of coagulation in cases of hemorrhagic purpura (3) there is more or less complete disappearance of jaundice in cases of hemolytic icterus (4) there is presumptive evidence of improved portal circulation in cases in which cirrhosis of the liver is present and (5) decreased amounts of urobilin and urobilinogen are found in the duodenal contents in hemolytic disease

Pathology

Most pathologists who are especially interested in study of the spleen agree that the organ is best preserved and that cellular differentiation is superior following slow injection of a fixative into the splenic artery

The spleen undergoes changes similar to those seen in many other organs These may be listed as follows atrophy senile changes chronic passive congestion inflammation (perisplenitis acute and subacute splenitis) abscess infarction focal necrosis hyaline degeneration and amyloid disease Brief mention will be made later of these various conditions

The pathologic changes of chronic splenomegaly can be considered under five headings (1) chronic fibrosis and vascular disease (2) reticulo-endothelial hyperplasia (3) lymphoid hyperplasia (4) myeloid metaplasia and (5) cysts and tumors

Chronic splenitis and chronic fibrosis with hypertrophy of splenic pulp usually are prominent in the pathologic picture of splenic anemia chronic infectious splenomegaly syphilitic splenomegaly chronic malarial splenomegaly kala azar splenomegaly of cirrhosis of the liver and mycotic splenomegaly Pathologic processes in the vessels of the splenic and portal system are common In some cases the onset seems to have been with splenomegaly and the blood vessels have become affected secondarily in others thrombophlebitic changes have occurred first and have led to chronic splenitis with splenomegaly and multiple infarction The blood vessels of the portal system should be studied as a part of the pathologic investigation of splenomegaly

McNee has stressed the importance of peri-ellipsoidal hemorrhage and nodular siderosis as a significant pathologic picture An extensive literature has accumulated on nodular siderosis the characteristic features of which have been called Gandy bodies although they were first observed by Stengel Out of confusion has come the probable fact that the peri-ellipsoidal nodules are the result of hemorrhage and fibrosis with deposition of iron in the elastic fibers The elastic fibers frequently appear jointed and resemble fungi Gibson has

Experimental Splenectomy —The important effects of experimental splenectomy may be summarized as follows, (1) anemia of the secondary type occurs, from which recovery takes place with hyperplasia of the bone marrow, (2) leukocytosis is produced which may be more or less persistent and which may be the result of removal of an inhibitory effect on the production of granular leukocytes (3) resistance of the erythrocytes to hypisotonic sodium chloride solution and other hemolytic agents is increased, (4) there is a lessened tendency toward experimental hemoglobinuria and jaundice after the administration of hemolytic agents (5) the volume of the portal blood is decreased, (6) there takes place conversion of yellow bone marrow into red marrow and actual increase in the volume of the marrow, which seems to be in excess of that which is necessary for compensation of the postsplenectomy anemia, and (7) hypertrophy of lymphoid tissue takes place and seems to be due principally to hyperplasia of reticular cells For a complete discussion of experimental splenectomy the reader is referred to the review of Krumbhaar

Physiologic Effect of Splenectomy on Man —The effects of splenectomy on man are as follows (1) anemia which is noted following experimental splenectomy performed on healthy animals is not ordinarily observed following splenectomy on man for pathologic conditions of the spleen, however mild anemia has occurred as the result of splenectomy for simple tumors of the spleen in otherwise normal persons ( ) leukocytosis is almost always present following splenectomy performed on man this leukocytosis is due to increase in the proportion of granular cells and has been noted months and even years following the operation (3) a slight increase in the resistance of erythrocytes has been noted following splenectomy for various conditions in hemolytic icterus, although increased fragility is still present following splenectomy, it has been noted that this fragility is less marked in some cases (4) the jaundice of hemolytic icterus disappears remarkably after splenectomy, but it is not known whether or not jaundice is more difficult to produce by hemolytic agents after splenectomy for other diseases, (5) a decrease in the volume of portal blood following splenectomy is suspected because of disappearance of ascites decreased incidence of gastro intestinal hemorrhage and improvement in the results of the dye retention test of hepatic function (6) direct observations have not been made on the volume of red marrow following splenectomy in man and (7) hyperplasia of lymphatic tissue has been seen occasionally in life and has been definitely found postmortem following splenectomy in man In addition to these analogies between experimental splenectomy and splenectomy in man there has been noted in man a definite increase in the number of reticulated erythrocytes and in the number of platelets in the circulating blood after splenectomy for various diseases The increase in the platelets is most marked following splenectomy for hemorrhagic purpura

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claimed that at least some of these cases are due to streptothrix Nodular siderosis occurs in a variety of diseases and is best regarded as a secondary vascular phenomenon

Reticulo endothelial hyperplasia or proliferation of the reticular cells of the spleen is seen most commonly in Gaucher s disease The same picture is found in other organs of the reticulo endothelial system The characteristic cells are large clear and striated The material in these cells recently has been shown to be a complex lipoid A similar pathologic picture is found in Niemann s disease and in Christian s syndrome and the storage of lipoids and neutral fats occurs in the lipemia of diabetes mellitus Reticulo endotheliosis with splenomegaly may be seen as monocytic leukemia

Lymphoid hyerplasia is seen in lymphatic leukemia, and as a secondary manifestation in lymphosarcoma and in Hodgkin's disease Two types are recognized from the pathologic standpoint, in one there is hyperplasia of the splenic nodules with compression of the pulp, in the other, the splenic pulp also becomes filled with lymphocytes and other types of lymphoid cells Lymphocytes may develop under abnormal conditions, wherever undifferentiated mesenchymal cells are present Although the term is not frequently used in the literature actual lymphoid metaplasia may occur in the splenic pulp The so called secondary nodules which may be found in the splenic nodules as well as in lymph nodes elsewhere have been regarded as active germinal centers but it is possible that they are pathologic structures resulting from irritation or centers for the destruction of lymphocytes

Myeloid metaplasia is seen in leukemia severe anemia, severe infection and chemical poisoning which is accompanied by active hemolysis It may be present normally in young infants and may be found in the spleens of infants with many diseases which cause anemia where it is an exemplification of the facility with which reversion to the fetal type of hemopoiesis occurs Myeloid elements chiefly myelocytes and megakaryocytes develop in the pulp Myelocytes are found also in the nodules indeed the splenic nodules may be partially obliterated There is evidence that the myeloid cells may develop from both undifferentiated lymphoid cells and from fixed reticular cells

Cysts and tumors which will be considered later can be listed as follows simple cyst polycystic disease echinococcus cyst, hemorrhagic cyst angioma, fibroma sarcoma and malignant metastasis

The pathologic picture seen in polycythemia vera is that of extreme congestion with thrombosis of the smaller vessels true metaplasia has not been observed in erythremia In hemolytic icterus the spleen usually is moderately enlarged and here again there is considerable congestion of the splenic pulp similar to that seen in chronic passive congestion and in pernicious anemia some pathologists suspect hemolytic icterus when in this type of spleen the

venous sinuses are small In pernicious anemia and in hemolytic icterus the reticular cells usually are increased in size and number and contain large amounts of pigment The microscopic characteristics described by Banti which by some are held to be characteristic of Banti s disease have been observed in other types of primary splenomegaly and in splenomegaly of cirrhosis of the liver These characteristics are diffuse fibrosis involving both the splenic nodules and the pulp narrowing of the venous sinuses endophlebitis of the splenic and portal veins and the Laennec type of cirrhosis of the liver Splenic anemia is now generally used as a clinical term in preference to Banti s disease and it has not been possible to demonstrate that Banti s pathologic criteria are constant or peculiar to this disease

Additional notes on pathology will be found in the comments on the various diseases

Examination of the Spleen and the Distinction between Splenomegaly and Other Tumors

One cannot be sure that the spleen is enlarged unless it can be palpated Frequently, however the suspicion of splenic enlargement can be aroused by percussion In distinguishing splenomegaly from tumor of the kidney of the pancreas of other retroperitoneal structures of the colon and of the stomach it may be of assistance to demonstrate the presence or absence of characteristic splenic dulness and the obliteration of Traube s space The physical characteristics of enlarged spleen are however most important Spleens that are slightly or moderately enlarged not only have palpable edge or notch or both and a smooth surface but seem to float on a wave with inspiration and give the sensation of being close to the costal edge and abdominal wall Slight enlargement of the spleen may be demonstrated by having the patient place the left hand and forearm beneath the body transversely in the lumbar region as he lies supine Usually however it can be palpated by standing to the right of a supine patient and with the left arm in front of the patient lifting the lower portion of the thorax forward with the left hand and at the same time palpating with the fingers of the right hand allowing the right hand to float as it were on the crest of the wave during inspiration the edge of the spleen sometimes will be found far out in the loin In my experience the slightly enlarged spleen may be felt most frequently after the patient coughs while lying on his right side

The shadow of the spleen obtained roentgenologically also can assist in diagnosis and dilation of the colon by air may give additional information for it is unusual for the colon to lie over any portion of the spleen occasionally it is attached to the anterior surface of the lower portion Certainly in any

questionable case, pyelography or urography should be resorted to, occasionally renal tumor and splenomegaly occur concomitantly and abnormalities of the renal pelvis from pressure may lead to a false suspicion of renal tumor A history of removal of a testis or the presence of a testicular tumor is presumptive evidence in favor of retroperitoneal tumor Tumors of the stomach and colon may possess a palpable edge or notch but can be excluded by roentgenology I have seen hair ball of the stomach with characteristics of a transversely placed spleen and carcinoma of the stomach with the contour of the spleen A tumor which bulges anteriorly is more likely to be of the pancreas or other retroperitoneal structure Retroperitoneal lipoma and primary retroperitoneal sarcoma are to be considered When bilateral renal enlargement is found polycystic disease may be present, and echinococcus cyst may be recognized by the complement fixation test of the blood and often by the form of calcification revealed by X ray It must be remembered that occasionally an enlarged spleen is markedly lobulated, and a spleen with a long pedicle may be moved to various positions in the abdomen, or may be more or less fixed in the lower portion of the abdomen or in the pelvis Exploration for pelvic tumor has disclosed splenomegaly The spleen may be very small or even absent Transposition of the viscera may cause confusion at first A palpable spleen in childhood may not be enlarged Slight enlargement in childhood may be associated with many diseases, and when essential data are negative, can safely be regarded as secondary and possibly of temporary nature

Roentgenologic Examination of the Spleen — The splenic shadow usually can be identified in good films taken for possible renal lesions In taking films especially to disclose evidence of disease of the spleen it is well to rotate the body slightly to the left to obtain the proper degree of penetration Shadows are seen occasionally in the splenic region doubtless due to calcified tubercles and to perisplenitis with calcification Examination of the spleen after injection of air or oxygen into the peritoneal cavity has not come into extensive use chiefly because of lack of pressing necessity for this examination and because of the slight risk of the procedure

Roentgenologic Examination of the Bones — Study of the bones in cases of splenomegaly has assumed increased importance in recent years The bones should be given careful consideration in the general examination of every patient with marked splenomegaly and on the slightest provocation roentgenograms should be made Roentgen ray examination is indicated in every case in which Gaucher s disease is suspected and in all cases of marked infantile splenomegaly The changes found are described under the various diseases In addition to Gaucher s disease they are found in tuberculosis syphilis rickets Niemann s disease, Christian s syndrome marble bone disease chloroma and myeloma

Splenic Puncture and Biopsy of Marrow — Splenic puncture carries a slight risk because of the difficulty of entirely preventing respiration during puncture It may be justifiable in suspected Gaucher s disease those who have practiced it say that the stage should be set for prompt operative procedure if hemorrhage results Biopsy of the bone marrow doubtless should be practiced more frequently removal of tissue from the sternum is simple and without risk and something may be learned especially concerning the regenerative activity of the bone marrow and the diagnosis in questionable cases

Examination of the Blood — Much may be suspected from careful consideration of the blood count and from a study of the morphology of the blood cells An extremely high hemoglobin index suggests pernicious anemia A persistent index of 0 8 or 0 9 suggests hemolytic icterus especially when slight leukocytosis and evidences of active regeneration are present that is moderate increase in percentage of polymorphonuclear cells a large number of reticulated erythrocytes and much polychromatophilia Microcytosis is an outstanding feature of hemolytic icterus A low index may be associated with many diseases in which there is a secondary type of anemia Leukopenia may occur with splenic anemia acute leukemia aplastic anemia and agranulocytosis morphologic study of blood smears is most important The leukopenia may be so extreme that the finding of stem cells only may enable the diagnosis between acute leukemia and agranulocytosis to be made A persistently low platelet count with signs of active regeneration suggests hemorrhagic purpura whereas a low platelet count with little if any regeneration suggests aplastic anemia Evidences of active regeneration may be significant in deciding in favor of splenectomy especially when doubt exists between a diagnosis of hemorrhagic purpura and aplastic anemia

Long coagulation time of blood removed from the vein is a characteristic of hemophilia Prolonged bleeding time and non retractile clot are important features in hemorrhagic purpura aplastic anemia and acute leukemia

In fact a complete blood count including a differential count, estimation of the percentages of reticulated cells and platelets and careful morphologic studies of blood smears by a person competent to make them are essential in the study of diseases associated with splenomegaly The Wassermann or a similar test and clinical investigation for syphilis should always be carried out Also it may be necessary to examine for fragility of erythrocytes coagulation time bleeding time calcium coagulation time prothrombin time retractility of clot viscosity of blood blood volume and concentration of serum bilirubin Blood culture and a dye retention test for hepatic function also may be advisable Blood grouping may save time and confusion following operation For detailed information it is necessary to refer the reader to the textbooks on clinical microscopy

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all degrees of modification of the foregoing characteristics may be present as results of cholecystitis gall stones and cholangeitis

Hemolytic Crises — A history of crises is obtained in cases of severe types of the disease crises of such extreme severity as to have produced hemoglobinuria have been reported However as the milder cases are recognized more generally the incidence of severe crises decreases Hemolytic crises are characterized by increased jaundice enlargement of the spleen fever headache nausea epigastric distress and sometimes vomiting The attacks may last for one or two days or for ten days they may date from infancy or childhood and gradually may get more severe culminating in later years in typical biliary colic with gallstones

Biliary Colic — In every case of biliary colic in which there is a palpable spleen the existence of hemolytic icterus must be excluded Cholecystitis is very common and gallstones are present more frequently than would be indicated by a history of colic but colic is by no means infrequent In hemolytic icterus the pain is almost always associated with increased jaundice and possibly with fever and chilliness but this cannot be interpreted as necessarily indicative of stone in the common bile duct in fact obstruction of the common bile duct is not common in association with the cholecystitis of hemolytic icterus In 118 cases of hemolytic icterus in which operation was performed at the Mayo Clinic from June 30 1911 to January 1 1931 evidence of disease of the gall bladder was reported in 81 (68 6 per cent) with no instance of stone in the common bile duct in 49 cases (41 5 per cent) gallstones were found

Anemia — This condition may be very mild and in advanced cases it may be so severe that it may simulate pernicious anemia I have seen cases with less than a million erythrocytes in each cubic millimeter of blood Usually there is moderate anemia and quite frequently a color index of 0 8 to 0 9 Slight leukocytosis occurs often The relative percentage of polymorphonuclear cells is increased Active regeneration is also indicated by an enormous increase in the number of reticulated erythrocytes 10 to 40 per cent of reticulated cells is common I have observed 85 per cent All of the morphologic features of active regeneration are prominent

Microcytosis — This characteristic of the blood deserves separate consideration to emphasize the importance of direct morphologic study of blood smears by the attending physician himself Microcytosis is so definite and characteristic a feature of hemolytic icterus that a presumptive diagnosis can be made without other data The cells are from 4 to 6 microns in size and uniformly dark and spherical Whether microcytosis is present at all times in definite degree and in milder cases cannot at this time be stated however when it is present it is a most important diagnostic feature Microcytosis persists after splenectomy it has been suspected but not proved that the microcytes are biconcave rather than spherical in some cases following operation

Hemolytic Icterus

This will be found discussed also in chapter XVI of vol II and in chapter V of vol III Fundamentally, hemolytic icterus is the outstanding example of hemolytic disease Periods of enormous degrees of destruction of blood exert little deleterious effect at least for many years, on the regenerative powers of the bone marrow It may be defined as a hemolytic disease with hemolytic crises and varying degrees of anemia and acholuric jaundice, active regeneration of the blood, splenomegaly, increased fragility of erythrocytes and in half of the cases, gallstones as a secondary development Familial, congenital and acquired types have been described However little clinical or laboratory distinction can be recognized in most of the typical cases In my experience the time of onset of symptoms has been in infancy, at eight years of age at puberty and, in a small group at the age of eighteen or twenty years In very few instances has the onset occurred later in life and when it has done so, it was necessary to guard against a mistake in diagnosis, especially with respect to cirrhosis of the liver associated with hemolytic anemia Unless one regards the cases in which the onset is in adolescence as cases of acquired hemolytic icterus the group of cases of truly acquired disease must be very small In these cases with onset at adolescence in view of the identical results of clinical and laboratory examination it would seem likely that congenitally some factors were present which later became pronounced Increased fragility of erythrocytes has been demonstrated in some of the relatives of adolescent patients It is not surprising that in cases with familial and congenital features the disease should be more severe

Diagnosis — From a diagnostic standpoint hemolytic icterus is the most important and most interesting of the chronic blood dyscrasias associated with splenomegaly When the data essential to a diagnosis of hemolytic icterus have been accumulated one has at hand the information necessary to a diagnosis of most of the other diseases in which chronic splenomegaly is present These data will be considered seriatim

A History of Jaundice — Jaundice may be absent at the time of examination, the concentration of serum bilirubin even may not be increased Usually, however jaundice either is present continuously, with exacerbations, or intermittently since an early age In some cases it dates from infancy, in others from childhood and in still others it is not first noted until the patient is eighteen or twenty years of age The jaundice is lemon yellow and the van den Bergh reaction is indirect unless complications of the biliary tract have supervened The jaundice of uncomplicated hemolytic icterus is of acholuric type There is no bile in the urine, and bile is present in the stools Pruritus is not present and there is no change in the coagulability of the blood But

designated hemolytic icterus True hemolytic icterus may manifest its symptoms first at any age even in old age but in these occasional cases the clinical characteristics are clear Unless therefore one chooses to regard the condition which affects adolescents in which a family history cannot be obtained, as acquired the group becomes very small

Wassermann Test — A serologic test for syphilis is essential in all diseases associated with splenomegaly In hemolytic icterus the Wassermann test occasionally may be strongly positive when no indications of syphilis are present on detailed investigation The Wassermann test in these cases has become negative after splenectomy and so far as is known manifestations of syphilis have not developed subsequently The reaction is evidently due to abnormalities in the blood associated with active hemolysis Syphilis and hemolytic icterus may be coexistent

Pathologic Physiology — The spleen in hemolytic jaundice is moderately enlarged Its color is dark red and microscopically the most prominent feature is diffuse congestion of the pulp similar to that of chronic passive congestion and pernicious anemia The splenic sinuses however are narrow and irregular and there is apparent increase in the number and size of the reticular cells which contain large amounts of pigment Increased fragility of erythrocytes and enormously excessive hemolysis are important fundamental features of hemolytic icterus It has been shown that normally all parts of the reticulo-endothelial system are concerned with hemolysis particularly the bone marrow In hemolytic icterus one may postulate abnormal activity of the spleen especially because the erythrocytes are easily laked and fragmented The spleen may to an abnormal degree prepare the erythrocytes for destruction both by fragmentation and by lysis and the actual destruction with liberation of pigment may occur chiefly in other parts of the reticulo-endothelial system The fact that hemolysis becomes reduced to normal limits in almost every instance after splenectomy indicates a most important part for the spleen to play and one well worth special investigation

Treatment — Many patients who have mild hemolytic icterus have good general health and do not need treatment Others occasionally may need instruction with respect to a diet efficient in cases of anemia The diet contains beef liver kidney apricots peaches prunes and the various food rich in vitamines The administration of iron is of questionable value because of the fact that *the cells of the reticulo-endothelial system are already overloaded* with iron as a result of hemolysis In severe cases transfusions may be necessary as a temporary measure However reactions are common following transfusion for hemolytic icterus and acute hemolysis may occur in spite of proper matching of blood

In both severe and moderately severe cases splenectomy should be re

Fragility — A most constant feature of the erythrocytes is increased fragility to hypotonic salt solution Fragility should always be tested against a control of normal blood to avoid technical error Initial hemolysis occurs at markedly higher concentrations of salt than is characteristic of normal blood, and complete hemolysis at definitely higher concentrations in almost every case Mild cases are seen in which initial hemolysis occurs in high concentrations of salt, but complete hemolysis is at the normal concentration Mild cases may be observed in which the results of the fragility test are entirely normal but I have not observed increased resistance in an uncomplicated case In a few cases fragility has been normal before operation and increased afterward Increased resistance is seen in hemolytic icterus only when chronic biliary jaundice of extreme grade is present and then rarely It is not known whether the bile interferes with the test or whether it actually decreases the permeability of the envelope of the erythrocytes

Splenomegaly — The spleen always is enlarged occasionally, however, it is not palpable Usually it is moderately to markedly enlarged rarely huge The spleen increases in size in periods of increased hemolysis The liver frequently is palpable but chronic cirrhotic changes are somewhat rare, and there is seldom any retention of the dye in the test of hepatic function

Familial and Congenital Types — In the familial type of the disease there are no major variations from the congenital type Families have been reported in which six living members were subjects of the disease It is transmitted through both males and females The erythrocytes of some members of these families clinically symptomless have been known to be of increased fragility, and it has been suspected that this abnormality of the erythrocytes is an important feature in transmission Splenomegaly without jaundice may be present Some members of families with hemolytic icterus may be lacking in general health and resistance particularly if manifestations of the disease have been severe in childhood This is also true of patients with congenital forms of the disease That there is however no fundamental difference between familial congenital and adolescent types is borne out by the fact that in some of the families in which there is a tendency to hemolytic icterus certain members may not have prominent features of the disease until they are twelve or even twenty years of age

Acquired Types — It has always been somewhat questionable whether or not most of the cases reported as instances of the acquired type of hemolytic icterus are not in reality either cases of biliary cirrhosis with hemolytic anemia or cases of biliary cirrhosis in the presence of potential hemolytic icterus Many of the features of hemolytic icterus are absent in these cases notably increased fragility of erythrocytes and microcytosis The hemolytic type of jaundice is seen in other diseases and is only one feature in the diagnosis of the entity

PRIMARY SPLENOMEGALY WITHOUT ANEMIA

Slight enlargement of the spleen is seen rather commonly in otherwise normal natives from southeastern Europe and the American tropics It has been assumed that this is secondary to malaria in childhood and that it needs no treatment

A moderate or marked degree of splenomegaly is seen not infrequently without significant symptoms The various diseases associated with splenomegaly may have been excluded and no adequate cause for the enlargement of the spleen discovered Slight if any anemia may be present yet the spleen is considerably enlarged These cases have been classified as potential splenic anemia and if enlargement of the spleen can be proved to be persistent and not markedly susceptible to radiotherapy splenectomy should be advised because marked chronic splenomegaly with fibrosis may lead to cirrhosis of the liver dilatation and degeneration of the associated vascular channels gastro-intestinal hemorrhage and anemia The risk of early removal is small It should be remembered that prolonged repeated treatment by roentgen rays is likely to increase adhesions and raise the operative risk

SPLENIC ANEMIA AND THE BANTI SYNDROME

In its simplest form splenic anemia consists of primary splenomegaly with a secondary type of anemia indeed even primary splenomegaly without anemia may be regarded as potential splenic anemia In its most advanced form marked pathologic changes in the liver develop with ascites and not infrequently with secondary portal thrombophlebitis and thrombosis Splenic anemia might be called cirrhosis of the spleen in analogy to cirrhosis of the liver

European writers recognize three stages of Banti s disease (1) splenomegaly with anemia (2) splenomegaly anemia and cirrhosis of the liver with or without gastro intestinal hemorrhage and (3) a more advanced grade of the second stage with ascites and portal thrombophlebitis and thrombosis Clinical experience however leads to the recognition of all degrees of pathologic involvement from splenomegaly without anemia to the most advanced involvement of portal system spleen and liver In fact cases are seen in which cirrhosis of the spleen and cirrhosis of the liver seem to develop concomitantly The disease is chronic and its duration from the earliest recognition of splenomegaly to the final stage usually is more than ten years Much depends on the time at which impairment of the liver develops

Splenic anemia is accompanied by a low color index leukopenia is the rule but is by no means constant the differential count reveal normal percentages

sorted to without unnecessary delay. This measure is curative and in experienced hands does not carry a high risk. In some cases in which there is debility, recovery to robust health cannot be expected. In the presence of cholecystitis, unless the cholecystitis is acute, splenectomy should be done first and cholecystectomy later; if splenectomy proves not to be difficult cholecystectomy may be performed at the same operation. Cholecystectomy has not been known to effect cure in hemolytic icterus, but cholecystitis has been quiescent for years following splenectomy. Splenectomy should be urged in well marked cases in childhood, especially if there is evidence of developmental retardation; debilitated children become robust after operation and the operative risk among patients less than ten years of age is almost nil. Women with hemolytic icterus usually pass through pregnancy and labor without severe anemia developing, and ordinarily splenectomy is not indicated in the course of pregnancy. Occasionally severe anemia develops in these cases toward the end of pregnancy, and repeated transfusions become necessary.

Splenectomy should not be performed in the course of a period of acute hemolysis; the patient should be allowed to recover from the crisis and there should be definite evidence of improvement in the anemia before surgical treatment is undertaken. I have seen no deaths as a result of postponement but have seen one patient die who was operated on while in a period of crisis. The picture at death was that of shock with hyperpyrexia. After splenectomy there occurs very rapid increase in the number of erythrocytes. This increase is much greater than appears from the count, for it has been shown that a concomitant increase in blood volume occurs which masks the true count by reason of a relative increase in plasma. Recovery from anemia and disappearance of jaundice are spontaneous after splenectomy without special medication.

From June 30, 1911, to January 1, 1931, 118 patients with hemolytic jaundice were operated on at the Mayo Clinic. The deaths in hospital were 4 (3.4 per cent). One hundred nine patients have been traced and in this group there were 11 subsequent deaths. Of the remaining 98 living patients 82 have reported themselves to be in satisfactory health, 1 in fair condition and 4 in poor condition. The results of splenectomy for hemolytic icterus therefore seem to be satisfactory, particularly when one takes into account that a certain number of the patients with familial and congenital conditions are not constitutionally robust. Of the 11 subsequent deaths one each was attributed to pneumonia, diabetes, meningitis, hemorrhagic smallpox (?) and "gangrenous dermatitis." There was one subsequent death following cholecystectomy. The remaining 5 patients died of conditions probably directly associated with hemolytic icterus: gastro-intestinal hemorrhage, anemia and cirrhosis of the liver. These deaths occurred in a period of twenty years.

Hemolytic icterus is distinguished by the following its familial or congenital features a history of recurring jaundice a history of hemolytic crises increased fragility of erythrocytes, microcytosis in which cells are spherical and evidence of marked regeneration on examination of blood smears with an increased reticulated erythrocyte count A patient with hemolytic icterus may present himself for examination at a period when jaundice is absent and in mild cases there may be normal fragility or very slight increase of fragility of erythrocytes

Only in recent years have clinicians been able to distinguish Gaucher s disease from splenic anemia The presence of a very large spleen dating from childhood, the not infrequent absence of severe anemia pathologic changes in the bones and pinguecula on the sclera all lead to the suspicion that the proper diagnosis is Gaucher s disease

Whether cirrhosis of the liver or splenic involvement has been primary frequently can be determined from the history and from the degree of involvement of the spleen at the time of examination A history of alcoholism in spite of statements to the contrary seems to be suggestive of primary cirrhosis of the liver as is also marked retention of dye in the absence of a very large spleen Recurring attacks of choluric jaundice with chills and fever favor a diagnosis of cholangeitis and hepatitis Although these features are common in cirrhosis they are seen only in the later stages of splenic anemia On the other hand there are cases in which cirrhosis of the liver and enlargement of the spleen seem to proceed hand in hand in other words spleno hepatic cirrhosis may be said to exist

Myelogenous leukemia may be seen when definite evidence of immaturity of cellular elements is absent from the blood For diagnosis a record of former examinations of blood may be necessary, although the skilled morphologist has little difficulty in suspecting myelogenous leukemia except in its very early stages Marked splenomegaly with the features of splenic anemia has been known to precede by several years the development of leukemia and leukemia has developed a year or more after splenectomy for what has seemed to be chronic splenomegaly of splenic anemia The presence of Hodgkin s disease and forms of lymphoblastoma when clinically confined to the spleen sometimes may be suspected because of contour on palpation Sarcoma may be suspected when other causes of splenomegaly have been eliminated from the presence of an irregular splenic tumor which has developed rapidly in an older patient Marble bone disease presents the clinical picture of splenic anemia but the bones of the body are markedly increased in density

The pathologic changes in the spleen in splenic anemia are essentially chronic fibrosis especially marked in the capsule and trabecula In addition Banti described fibrosis of the reticulum and of the follicles with atrophy of the follicles hyaline degeneration of the arterial walls and endophlebitis of the

or relative lymphocytosis morphologically the smears reveal marked poikilocytosis affecting about half the erythrocytes, and in some cases there is generalized, slight microcytosis Gross gastro intestinal hemorrhage occurs sooner or later in at least half the cases, and obscure bleeding doubtless more frequently The bleeding almost certainly arises chiefly at the lower end of the esophagus from esophageal varices where enormous venous spaces have been shown to lie directly beneath the mucous membrane and from enlarged veins of the cardiac portion of the stomach It is not possible to say that the anemia is entirely due to hemorrhage the extreme poikilocytosis, which amounts almost to fragmentation of cells suggests that there is direct action on the erythrocytes

The diagnosis of splenic anemia is in the last analysis made by exclusion Clinicians have learned to distinguish cases of syphilitic splenomegaly, chronic infectious splenomegaly primary portal thrombophlebitis and thrombosis, hemolytic icterus Gaucher s disease and other rare diseases

Syphilitic splenomegaly usually is associated with syphilitic hepatitis, a strongly positive Wassermann test and other evidence in the history and the examination in favor of the diagnosis of syphilis A strongly positive Wassermann test in itself is not however sufficient for a diagnosis cases of hemolytic icterus have been seen in which a strongly positive Wassermann test has become negative following splenectomy and in which a diagnosis of syphilis could not be made otherwise

Chronic infectious splenomegaly as a result of chronic recurring infection that has existed over a period of years may present a clinical picture which cannot aside from the history be distinguished from splenic anemia Yet it is known that these patients do not improve satisfactorily following splenectomy A syndrome similar to splenic anemia has been reported especially in association with recurring furunculosis arthritis endocarditis recurring peripheral phlebitis ulcerative colitis and portal thrombophlebitis

Portal thrombosis may occur late in the course of splenic anemia Portal thrombosis resulting from primary portal thrombophlebitis however occurs early and there is subsequent gradual development of splenomegaly In portal thrombophlebitis portal thrombosis may recur over a period of many years and canalization of vessels may take place Moderately severe generalized abdominal pain with tenderness and distention but without signs of localization associated with intermittent fever of long duration and with the presence of definite firm and sometimes marked splenomegaly and with absence of other causes of fever may lead to the suspicion that the splenomegaly is secondary to primary portal thrombosis A history of recurring attacks of this kind may be obtained from a patient presenting the typical syndrome of splenic anemia, and a huge spleen may develop ultimately

Statistics emphasize the importance of splenectomy early in the course of the disease

Of 80 living patients, concerning whom information could be obtained 44 were living five years or longer of whom 21 were living ten years or longer after operations all of these patients except 5 were in good or fair health Of those who had died 13 had lived five years or longer and of these 7 had lived ten years or longer Several patients who died had lived as long as twelve fourteen and eighteen years after operation Three patients are living in good health eighteen years after splenectomy

Splenectomy decreases the likelihood of subsequent gastric hemorrhage In a group of 167 cases of splenic anemia preoperative hemorrhage had occurred in nearly 60 per cent Postoperative gastric hemorrhage was found to occur in 35 per cent and the cases in which hemorrhage did not occur following operation constituted more than 65 per cent It would be expected that in some cases in which preoperative hemorrhage had not occurred with advance of the disease gastric hemorrhage ordinarily would have developed It can be concluded therefore that splenectomy most likely decreases the probability of the later occurrence of gastric hemorrhage Ligation of the coronary vein of the stomach has been proposed as treatment for postoperative gastric hemorrhage but the number of cases in which this has been done has been small and the results are not conclusive

Medical or preoperative treatment may consist of measures necessary in the care of gastro intestinal hemorrhage in the treatment of the anemia and in advanced cases in treatment of cirrhosis of the liver and ascites The customary measures for hemorrhage such as absolute rest in bed withdrawal of food and sedatives are necessary Transfusions and administration of from 4 to 6 gm (60 to 90 grains) of ferric citrate daily together with a proper diet are essentials in the treatment of anemia Administration of acid producing salts such as ammonium nitrate and salyrgan together with a diet low in protein and salt and restriction of water may be remarkably effective in eliminating fluid and in improving the hepatic function and the patient s general condition

Chronic Infectious Splenomegaly

In view of the fact that patients with splenomegaly and anemia associated with a history of chronic recurring infections or septic conditions have been known to benefit less from splenectomy than patients with uncomplicated cases of splenic anemia it seems wise to classify them separately This should not lead to the inference that splenic anemia may not be due to an infectious process localized chiefly in the spleen At the time of examination the features of a given case may be those of splenic anemia but a history of recurring tonsillitis

splenic vein Variations of these pathologic changes are present in other diseases notably in cirrhosis of the liver and syphilis It has not been demonstrated that there is a pathologic picture which is pathognomonic of Banti disease The cirrhotic changes in the liver are eventually of the atrophic type and the finding of hyperplastic red bone marrow has been reported at necropsy

In 94 cases the size of the liver was noted at operation in the series at the Mayo Clinic, in 23 per cent of these it was small, in 43 per cent, normal and in 34 per cent, large With few exceptions, there was definite evidence of cirrhosis of the liver irrespective of size In some instances tissue from the liver on microscopic examination revealed only hepatitis

The treatment of splenic anemia should be directed mainly toward conservation of the function of the liver Therefore, early removal of the spleen seems to be most important Even in cases of potential splenic anemia when moderate splenomegaly is present without anemia, the operation seems to be advisable The operative risk in early cases in which the spleens are only moderately enlarged is small After the development of marked perisplenitis, sclerosis of splenic vessels and impairment of hepatic function the operative mortality may be very high and the likelihood of beneficial results decreases

Splenectomy decreases the amount of blood passing through the liver it decreases although it does not eliminate the frequency of hemorrhage by removal of dilated vessels and almost certainly it removes or modifies a splenic factor in destruction of blood Nevertheless, it will not seem advisable to submit every patient to surgical treatment Older patients especially may be nursed along to much better advantage when an advanced stage of the disease is present especially if a dye retention test indicates much impairment of hepatic function or if cardiovascular complications are present On the other hand some remarkable results have been reported in advanced cases with ascites, but chiefly among patients less than fifty years of age Ascites usually recurs after splenectomy but frequently disappears later, presumably with improvement in portal circulation and in hepatic function

Of patients at the Mayo Clinic who had been subjected to splenectomy between December 31 1908 and January 1 1931 167 were classified as having had splenic anemia The deaths in hospital numbered 16 a mortality of approximately 10 per cent One hundred forty eight of these patients have been traced Of these 68 have died 80 are living and of these 63 report themselves to be in satisfactory health It should be noted that the 86 deaths occurred in a period of twenty two years Subsequent death has been attributed in most of the cases to cirrhosis of the liver and to hemorrhage One cannot promise in the individual case therefore that pathologic processes in the liver will be checked or that hemorrhage will be eliminated by splenectomy

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arthritis endocarditis, furunculosis, phlebitis, ulcerative colitis or portal thrombophlebitis may be obtained The infectious process may have injured the function of the vascular and renal structures to such a degree that splenectomy will have little if any effect on the recurring infectious process Most of the infectious processes leading to spenomegaly and anemia are easily recognized however the frequency of the relationship between ulcerative colitis portal thrombophlebitis and splenomegaly has been appreciated only lately Primary portal thrombosis as an etiologic factor may be unsuspected, except in those cases in which a clear-cut history of recurrent, generalized, abdominal pain with remittent fever is obtainable Confusion is caused also by the fact that portal thrombosis may occur with any form of splenomegaly, especially with splenic anemia late in the course of the disease as a secondary manifestation In the cases I refer to as instances of chronic infectious splenomegaly portal thrombophlebitis is probably the primary condition at least thrombosis is antecedent to splenomegaly In portal thrombophlebitis the spleen may be only slightly enlarged, or it may be enormous It may contain infarcts, and at postmortem examination the portal vessels may show evidence of recurrent thrombophlebitis, thrombosis and canalization The history of recurrent portal thrombophlebitis may be of long duration I know of one case in which the history was of twenty years duration and in which at necropsy the most extreme involvement of the portal system with chronic canalization of the vessels was present, and the spleen was of enormous size Patients who present the syndrome of splenic anemia and a history of diarrhea should be examined thoroughly for evidence of ulcerative colitis Sometimes the colitis is limited to one portion of the colon, the associated splenomegaly is almost certainly of secondary infectious nature, and removal of the spleen becomes of questionable value

Removal of the spleen for acute or subacute infectious processes has not definitely benefited the course of the disease and in chronic infectious diseases usually it has not materially altered the progress of the pathologic processes

In this group of cases operative mortality has been high and subsequent death frequent Death has been due to portal thrombosis, ulcerative colitis, cardiorenal disease and hemorrhage Treatment should be directed toward controlling the recurrence of infection and conserving the function of vital organs Only in cases of milder infection should splenectomy be undertaken, and then only when anemia or recurrent gastro intestinal hemorrhage are important features of the condition and when there is evidence of satisfactory function of the liver

From July 2 1908 to January 1 1931 32 cases in which splenectomy was performed and which were classified as instances of chronic infectious splenomegaly were seen at the Mayo Clinic The deaths in hospitals numbered 8 (25

per cent) Of the remainder of the patients only 8 are living and of these 6 are in satisfactory health

Clearly if this group of cases of splenomegaly is included with the cases of splenic anemia the figures which are supposed to represent the mortality and the morbidity following splenectomy for splenic anemia will be unjustifiably increased and an inaccurate conception of the value of splenectomy in splenic anemia will be formed

Primary Portal Thrombophlebitis

This condition has been mentioned in the preceding sections on splenic anemia and chronic infectious splenomegaly and it also appears in chapter VI of volume 3 Endophlebitis of the portal system is the primary pathologic process and attacks of thrombosis occur over a period of years resulting in canalization and in many cases in gradual development of splenomegaly The spleen may be very large and frequently contains old and new infarcts The splenomegaly of primary portal thrombophlebitis logically can be classified with chronic infectious splenomegaly A clinical diagnosis of course cannot always be made but when indications are suggestive splenectomy usually is not indicated

Cirrhosis of the Liver

Material on this condition was included in Chapter VI of volume 3 Attention should be called to the fact that cirrhosis of the liver and chronic splenitis may occur together and in certain cases it is impossible to determine whether cirrhosis or splenomegaly is the primary condition When the spleen is very large and evidence of satisfactory hepatic function can be demonstrated splenectomy usually is warranted even though it may appear that the cirrhosis of the liver is primary In cases in which the spleens are smaller and in which impairment of hepatic function is slight splenectomy combined with the Talma Morison operation may be undertaken Splenectomy is more likely to be beneficial in cases of cirrhosis of the liver which exhibit the following features hemolysis definite anemia evidence of active regeneration of the blood cells on morphologic examination of smears absence of fever and absence of signs of cholangeitis

In 43 cases in which cirrhosis of the liver apparently was primary splenectomy was performed at the Mayo Clinic Only 14 of the patients are living and of these only 4 are in good health Of these 4 cases retention of dye on test of hepatic functions was graded in 2 cases and was graded 0 in 2 cases the good results may have been due in part to satisfactory hepatic function

In 7 of the 43 cases a Talma Morison operation also was done, 3 of these patients are living six years two years and one year respectively, following operation, in fairly satisfactory health

HEMOCHROMATOSIS

Hemochromatosis is considered in chapter VIII of volume 4 The spleen may be of normal size slightly enlarged or markedly enlarged very much as occurs in association with cirrhosis of the liver There is diffuse increase in connective tissue and in addition to the evidences of chronic splenitis and passive congestion the phagocytic cells of the spleen are engorged with pigment This pigment consists of an iron containing substance, hemosiderin and a non iron reacting material hemofuscin Discovery of a combination of pigmentation of the skin hepatic cirrhosis and glycosuria, with exclusion of argyria and Addison s disease leads to proper diagnosis The diagnosis of hemochromatosis however may be difficult previous to the development of the typical characteristics Splenectomy has not been performed in hemochromatosis and there is no a priori reason for anticipating any therapeutic effect other than that which might result from reduction of the amount of blood which passes through the liver

CHRONIC HYPERPLASTIC POLYSEROSITIS CONCATO PICK DISEASE

This disease is considered under the name of pericarditic pseudo cirrhosis in chapter VI of volume 3 Hyperplastic hyaline perisplenitis and perihepatitis occur in some of the cases of polyserositis and secondary chronic splenitis and cirrhosis of the liver develop The spleen in some of these cases becomes considerably enlarged and it is necessary to distinguish the condition from splenic anemia and cirrhosis of the liver Splenectomy in this condition is very difficult and the operative risk is great This type of splenomegaly properly belongs in the group of chronic infectious splenomegaly in which splenectomy is of questionable value I have seen one patient with Concato Pick disease who underwent splenectomy and who died after operation In view of the frequency of cardiac decompensation in this syndrome pericardiectomy is probably a more logical surgical procedure

SYPHILITIC SPLENOMEGALY

Other material on this subject appears in chapter XXVIII of volume 5 There are cases of visceral syphilis in which splenomegaly is a prominent feature and variable degrees of hepatic involvement are present Outstanding anemia may or may not be present the clinical picture may be that of splenic

anemia but there is notable absence of gastro-intestinal hemorrhage. The Wassermann test is strongly positive in a high percentage of the cases and is a most important feature in diagnosis. A persistently positive Wassermann test rarely, if ever, is seen as the result of splenic anemia; only the strongly positive Wassermann test which occasionally results from hemolytic icterus need cause confusion. With hemolytic icterus excluded by its other features, a strongly positive Wassermann test in the presence of marked splenomegaly leads to exhaustive investigation for other evidence of syphilis and is usually found to mean either syphilitic splenomegaly or syphilis in conjunction with some other disease which causes splenomegaly. Several years ago it was noted at the Mayo Clinic that some of the patients with visceral syphilis and marked splenomegaly did not improve satisfactorily on antisyphilitic treatment; their general condition remained unsatisfactory and little improvement occurred in the anemia. It was decided to remove the spleen on the assumption that improvement in the condition of the liver might be more rapid. The response was even more satisfactory than had been anticipated. Antisyphilitic treatment became effective after splenectomy and recovery from the anemia was rapid. The positive Wassermann test, however, not infrequently persisted. In spleens removed there was evidence of chronic fibrosis both of the trabeculae and of the reticulum of the pulp. Small gummas were present and *Treponema pallidum* could be demonstrated in some of the spleens. Splenectomy is necessary only in the occasional case of visceral syphilis with splenomegaly, but when improvement has not occurred following medical treatment, the beneficient effect far outweighs the risk.

From December 4, 1914, to January 1, 1931, 10 patients with this type of splenomegaly were submitted to splenectomy at the Mayo Clinic. There was one death in hospital. Four patients have died subsequently, one from carcinoma of the uterus, one from pneumonia, one from portal thrombosis and one from a cause unknown eleven years after operation; one other of these four patients had lived eleven years. Five patients are living and are in satisfactory health. One has lived sixteen years and two others have lived fifteen years following operation.

Gaucher's Disease

Gaucher's disease is discussed also in chapter VII, Vol. 4, volume 4. Fundamental conceptions concerning the nature of Gaucher's disease have changed considerably in recent years. Originally described in 1882 as a form of epithelioma of the spleen, for many years it was regarded as a result of endothelioid hyperplasia. It is now recognized as a constitutional disease involving a fundamental disorder of metabolism in which a complex lipoid, kerasin, is deposited in the

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This disease is considered under the name of pericarditic pseudo cirrhosis in chapter VI of volume 3 Hyperplastic hyaline perisplenitis and perihepatitis occur in some of the cases of polyserositis and secondary chronic splenitis and cirrhosis of the liver develop The spleen in some of these cases becomes considerably enlarged and it is necessary to distinguish the condition from splenic anemia and cirrhosis of the liver Splenectomy in this condition is very difficult and the operative risk is great This type of splenomegaly properly belongs in the group of chronic infectious splenomegaly in which splenectomy is of questionable value I have seen one patient with Concato Pick disease who underwent splenectomy and who died after operation In view of the frequency of cardiac decompensation in this syndrome, pericardiectomy is probably a more logical surgical procedure

Syphilitic Splenomegaly

Other material on this subject appears in chapter XXVIII of volume 5 There are cases of visceral syphilis in which splenomegaly is a prominent feature and variable degrees of hepatic involvement are present Outstanding anemia may or may not be present the clinical picture may be that of splenic

mortality in this small series One patient died of cerebral hemorrhage six years after splenectomy and after having had a considerable period of good health The other three patients are living respectively two three and eleven years following splenectomy The patient of longest postoperative life has had four children since operation Fischer reviewed 41 cases from the literature The operative mortality was 19 5 per cent and some of the patients were living in good health six years others eight years and others thirteen years after operation It seems to be demonstrated therefore that even though splenectomy is not a curative measure it may afford great relief to the patient and arrest the progress of the disease

Marble Bone Disease

Moderate enlargement of the liver and spleen is present in marble bone disease (Albers Schonberg syndrome) Roentgenologically the bones appear to be very dense Splenomegaly is associated with anemia which is probably due to reduction of the volume of marrow In advanced cases symptoms may be present which are secondary to pressure of bone on the cranial nerves Secondary myeloid metaplasia is found in the spleen liver and lymph nodes Study of the blood reveals in addition to the anemia leukopenia, thrombocytopenia and occasionally the presence of normoblasts and myelocytes I have seen one case of this disease in which subsequently a blood picture suggestive of myelogenous leukemia developed this blood picture however may have been the result of extreme myeloid metaplasia

Malarial Splenomegaly

Malaria is considered in detail in chapter XXXII of volume 5 Splenomegaly is almost always present in both acute and chronic forms of malaria In acute cases the spleen frequently weighs from 300 to 500 gm and in neglected chronic cases from 900 to 1 500 gm Spleens weighing more than 5 000 gm have been reported In acute cases the spleen becomes engorged with blood plasmodia and macrophages containing detritus Rupture may occur either spontaneously or with very slight trauma In chronic enlargement of the spleen the long continued irritation leads to proliferation of connective tissue compression of the splenic nodules and marked dilation of the veins Perisplenitis is reported as a very common and painful complication

Malarial splenomegaly may assume the clinical characteristics of splenic anemia Not infrequently patients who were born in the countries of southeastern Europe and in the American tropics now living in the United States are found to have slightly enlarged firm spleens which because of the former prevalence

hyperplastic reticular cells of the hematopoietic system Pathologic changes may, therefore, be present in the spleen, liver, lymph nodes, bone marrow, bones and other organs The disease is similar to the spleno hepatomegaly of Niemann in which the abnormal metabolic product is a phosphatide and deposition of the phosphatide is not confined to the hematopoietic organs but may involve also muscle epithelial cells and nervous tissue Christian s syndrome is of similar nature and storage of lipoids occurs also with the lipemia of diabetes

Mandelbaum and Downey in 1916 established the pathologic histology of Gaucher s disease They demonstrated that the large cells arose from the reticulum of the hematopoietic organs The papers on Gaucher s disease by Brill and Mandelbaum are authoritative

The diagnosis of Gaucher s disease may be made with considerable accuracy in certain cases particularly if two or three children of the same family are affected and if all of the important characteristics are present These characteristics are as follows huge enlargement of the spleen dating from childhood leukopenia thrombocytopenia bleeding especially from the nose or gums, pigmentation of exposed areas of the skin lesions similar to pingueculæ appearing both on the nasal and the temporal sides of each sclera marked increase in the size of the liver with absence of ascites and particularly pathologic changes in the bones demonstrable roentgenologically In the early stages of the disease anemia is not a prominent feature The disease is much more common in females than in males, but it is not, as was formerly supposed, confined to persons of the Hebrew race Although pathologic changes in the bones may occur with other disorders of metabolism associated with splenomegaly and although metastatic malignant growths may be difficult to exclude nevertheless the abnormalities of the bones associated with Gaucher s disease are of great assistance in the diagnosis Widening of the marrow cavity mottling, osteoporosis regions of increased density destruction of a vertebra by pressure and even pathologic fracture may be present Changes in the bones are demonstrable roentgenologically in approximately 50 per cent of the cases and gross skeletal deformities in about 10 per cent The diagnosis of Gaucher s disease may be confirmed also by splenic puncture a procedure of considerable risk by biopsy of the bone marrow and by excision of an affected gland

Medical measures may be helpful in reducing the size of the spleen and in combating the anemia Treatment by roentgen rays is effective but must be given cautiously because of the fact that the skin of patients with Gaucher s disease burns rather easily The usual measures such as a blood building type of diet and large doses of iron are indicated for the anemia The exact value of splenectomy for Gaucher s disease has not been definitely determined

In the experience at the Mayo Clinic 4 women with well authenticated cases have been subjected to splenectomy Fortunately there was no operative

may be so much reduced as to give a rather high color index and normoblasts are present in the smears. Parasites may be found in the leukocytes in material obtained by splenic puncture or on examination of an excised lymph node. Intravenous injection of antimony sodium tartrate or antimony potassium tartrate reduces the mortality. Splenectomy has not yet been demonstrated to be of sufficient value to warrant the risk of operation.

Schistosomiasis

Schistosomiasis is considered in detail in chapter XXXVII of volume 5. Infestation by certain schistosomes causes a chronic disease associated with enlargement of the liver and spleen and frequently hematuria and bloody stools. It is not uncommon in Egypt and other portions of Africa as well as in the Philippines, China and Japan. The condition resembles either cirrhosis of the liver or splenic anemia. The spleen may be very large. The flukes live in the vessels of the portal system and ova may be found either in the urine or the stools. Occasionally they have been found in the circulating blood. I have seen no reports of splenectomy for this disease.

Splenomegaly with Anemia in Infancy
(Including von Jaksch's Disease)

I am considering under this heading the condition corresponding with cases that have been reported in the literature in which patients who were less than two and a half years of age have had well marked anemia associated with splenomegaly. After the age of two and a half years the clinical syndromes conform more nearly to those of the adult types of splenomegaly. Most of the cases in infancy have been reported as instances of von Jaksch's disease. The characteristics of this syndrome have been described as follows: (1) definite reduction both in concentration of hemoglobin and in number of erythrocytes; ( ) leukocytosis with both relative and absolute lymphocytosis; (3) the presence of a small number of myelocytes and metamyelocytes in the peripheral blood and in some of the cases a large number of immature erythrocytes; and (4) myeloid metaplasia, particularly in the liver and the spleen, marked hyperplasia of the splenic pulp and compression of the splenic nodules. None of these features has been constant and there has been great confusion in the diagnosis of von Jaksch's disease. Some of the reported cases have appeared, from the pathologic standpoint, to be cases of leukemia; others have been associated with malnutrition and rickets and still others with syphilis and tuberculosis. It is striking that cases conforming closely to the von Jaksch's syndrome have become much less common in large clinics in recent years with improvement in infant feeding in

of malaria in the areas of their birth have been suspected to be the result of that disease These patients usually do not have anemia the enlarged spleens are found incidentally Occasionally patients with marked splenomegaly and gastro intestinal hemorrhage, who have always lived in a temperate zone, give histories of having had malaria in childhood or adolescence In these cases the probability of the malaria having acted as an etiologic factor is uncertain On the other hand, from malarial geographic areas cases have been reported in which splenomegaly has become progressively more marked following malaria in childhood which had been cured

I have had no personal experience with splenectomy for chronic malarial splenomegaly but I have seen a few patients with splenic anemia who have given histories of malaria These patients have been benefited by splenectomy in the same degree as have others with splenic anemia It is reported however that recovery from malarial cachexia and anemia is, as a rule, satisfactory following removal of very large spleens in cases of chronic malaria Attacks of recurrent malaria have occurred following splenectomy, as in fact sometimes happens after any operation but the cases of postoperative malaria that have been reported have been controlled easily The reported mortality of splenectomy for chronic malarial splenomegaly is very high this is attributed to the difficulty of the operation caused by dense adhesions The operative mortality, however, doubtless will be reduced by preoperative and postoperative care and by simple exploration in difficult cases

Egyptian and Colombian Splenomegaly

Cases of splenomegaly occurring in Egypt and also in the American tropics have been described In these cases the etiologic factor has not been determined and malaria leishmaniasis and other forms of active parasitic infestation have been excluded The exact nature of these cases is not clear however it is likely that even though parasites are not present, the splenomegaly is secondary to former infestation or the result of chronic infectious processes Not infrequently the condition advances to take on the picture of advanced splenic anemia Splenectomy has been beneficial in some of the cases

Kala Azar

This condition is considered also in chapter XXXVI of volume 5 Splenomegaly is a prominent feature in both the adult and infantile types of infestation by Leishman Donovan bodies but the characteristics of the blood usually are not those of splenic anemia Although extreme leukopenia may be present there is great reduction of polymorphonuclear cells and the erythrocyte count

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able whether anything is to be gained by straining a point to make the diagnosis of von Jaksch s disease

The treatment of a case of splenomegaly associated with anemia in infancy largely depends on analysis of the probable fundamental factors in its etiology Clear cut cases of hemolytic icterus and hemorrhagic purpura almost certainly will be benefited by splenectomy If features of the cases conform to those of the adult type of splenic anemia and the process seems to be more advanced in the spleen especially if there is evidence of active regeneration in study of morphologic features of the blood splenectomy is likely to be definitely beneficial In cases of questionable etiology and doubtful classification the decision for or against splenectomy will depend chiefly on study of morphologic features of the blood If there are evidences of aplastic marrow splenectomy would not be expected to be of value If there is evidence of increased hemolysis and active regeneration splenectomy is to be considered

Proper feeding and hygiene are of the greatest importance A blood building type of diet together with administration of iron frequently is effective Transfusion of blood may be necessary Extensive feeding of adult liver and administration of liver extract are not to be encouraged in these secondary types of anemia

In the experience at the Mayo Clinic splenectomy for various causes has been done in six cases in which the patients were two and a half years of age or less the youngest patient was eight months of age Three of these cases were classified as instances of splenic anemia two as hemolytic icterus and one as subacute infectious splenomegaly The youngest patient with hemorrhagic purpura was aged four years There were no operative deaths The patient with subacute infection and one patient with splenic anemia died later The four living patients are in satisfactory health

Rickets

The main consideration of rickets is given in chapter X of volume 4 The spleen often is enlarged in children with rickets but does not demand direct treatment unless the syndrome of splenic anemia of infancy develops as a chronic condition Then the material given in the section on splenomegaly with anemia in infancy is applicable

Scurvy

In chapter XI of volume 4 scurvy is considered at length The spleen often is enlarged in scurvy and hemorrhagic infarcts are not uncommon Anemia may be extreme but it is of the simple type and the blood does not show dis

fant hygiene and diagnostic methods, in fact, so rare are the cases that the condition seems to be almost non existent It is possible that von Jaksch s disease is in the process of elimination as an entity In fetal life, formation of blood begins in the liver, is then taken up by the spleen and then by the bone marrow In a reversion to the fetal type of formation of blood, which might result from disorders of metabolism or from infection, stimulation of any of these organs would naturally lead to myeloid metaplasia in reverse order that is first in the spleen and last in the liver This process would account for the pathological picture described in so many of the cases that have been reported as instances of von Jaksch s disease

In the etiology of many of the cases of anemia associated with splenomegaly in infancy nutritional and metabolic factors and chronic infection are of primary importance rickets or syphilis is frequently the cause, or the syndrome may be that of Niemann s disease or Christian s syndrome Some conditions are familial notably hemolytic icterus and sickle cell anemia, the erythroblastic anemia of Cooley also should be considered in this connection True hemorrhagic thrombocytopenic purpura occasionally occurs, I do not refer to the perplexing group of cases designated as hemorrhagic disease of infancy The pathological process may be primary in the liver, and a diagnosis of cirrhosis of the liver may be warranted It is entirely possible, also, that a process which might cause the syndrome of splenic anemia in adults and children would, in infants, by reason of reversion to the fetal type of formation of blood, produce the features which have been reported in cases of von Jaksch s disease I have seen a patient four years of age with the clinical syndrome of the adult type of splenic anemia, whose condition a competent pediatrician had diagnosed as von Jaksch s disease when the patient was nine months of age

Morphologic study of the blood is of great importance in anemia of infancy Some of the cases of splenomegaly in infancy are associated with evidence of excessive destruction of blood and others with evidence of inadequate production of blood Evidences in the blood smears of active regeneration may be extremely important from a practical standpoint especially in deciding for or against splenectomy Patients who show active regeneration are more likely to be benefited by splenectomy Many of the morphologic features can be explained only by assuming that there is reversion to the fetal type of production of blood

The different types of anemia and splenomegaly of infancy constitute a confusing group of cases Many of them undoubtedly are explained by improper feeding nutritional disease and infection some are associated with inadequate formation of blood and others with excessive destruction of blood a few are due to primary cirrhosis of the liver and possibly a few to primary splenitis Cases of hemolytic icterus and of hemorrhagic purpura occur It is question

from a case of acute aplastic anemia here one must rely chiefly on evidence of normal regeneration of the blood which is present in hemorrhagic purpura Hemorrhagic features of leukemia may be similar to those of hemorrhagic purpura but morphologic study of blood smears reveals immature cells

The spleen may be moderately enlarged it is usually however just easily palpable and occasionally cannot be felt I have seen one case in which the spleen weighed less than normal at the time of operation yet the patient was symptomatically cured by splenectomy Occasionally the spleen may extend to the level of the navel

Certain features of the blood are most important from a diagnostic standpoint The platelets are consistently reduced in number and abnormal in morphology It is necessary to have daily platelet counts in order to establish a numerical level for occasionally the platelet count may be temporarily normal The citrate method is satisfactory for comparative counts although the absolute figures obtained are probably much less than actual normal figures Morphologically many of the platelets are large and irregular and it has been suggested that this deformity precludes efficient closure of vascular stomas The quality of the thromboplastic material produced by the platelets seems to be normal but its quantity is insufficient In hemophilia the platelets are deficient in quality but sufficient in number

In hemorrhagic purpura the bleeding time normally one or two minutes after simple acupuncture is definitely prolonged It may be four to eight minutes or may even be prolonged indefinitely

A low platelet count a prolonged bleeding time and delayed retractility of clot are the most important characteristics of coagulation in hemorrhagic purpura When blood is drawn into a Wassermann tube retraction from the wall of the tube usually occurs in one or two hours The blood of hemorrhagic purpura does not show evidence of retraction for several hours and retraction may not be complete in twenty four hours

The diagnosis of hemorrhagic purpura is so important in connection with treatment by splenectomy that a tabulation is inserted for reference (Table I)

In cases in which the clinical features are confusing hereditary hemorrhagic telangiectasia can be recognized or excluded by careful inspection of the mucous membranes hemophilia and acute leukemia can be eliminated by the history the features of coagulation and study of blood smears the decision then rest among hemorrhagic purpura acute aplastic anemia and hemorrhagic disease secondary to chemical poisons notably the arsphenamines Given the characteristic abnormalities of coagulation evidence of satisfactory normal regeneration on morphologic study of the blood is the most important single consideration in hemorrhagic purpura normal leukocyte count a normal percentage of polymorphonuclear cells a normal reticulated erythrocyte count polychromato-

tinctive morphologic features In infantile scurvy the spleen may be enlarged also but chronic splenomegaly rarely results, and splenectomy does not have a place in the treatment

Hemorrhagic Purpura

The hemorrhagic diseases including hemorrhagic purpura are considered in chapter XIX of volume 2 It may be well in this section to list certain features which are outstanding from the diagnostic standpoint, in view of the great importance of diagnosis in determining the advisability of splenectomy

Hemorrhagic purpura is an acquired hemorrhagic disease with certain definite features of deficient coagulation which lead to the synonym, 'thrombocytopenic purpura Whether the condition is idiopathic, the result of infection or of some product of infection has not been determined at best idiopathic is a term of little inspiration Some of the spleens removed in cases of hemorrhagic purpura have been the site of acute splenitis with inflammatory infiltration and an increase of polymorphonuclear cells Infectious purpura has many features in common with hemorrhagic purpura and it may be that infectious purpura becomes hemorrhagic and thrombocytopenic when the infectious or toxic product influences the spleen itself This conception of the disease is offered only as one theoretic explanation that is in line with clinical and pathologic features

The hemorrhagic features of the disease are most prominent Hemorrhage may be from any part of the body but is especially troublesome as epistaxis bleeding gums and metrorrhagia The chronic remittent type of hemorrhagic purpura with a history of from two to ten or fifteen years, has been reported most frequently but subacute cases and acute severe cases of one to four weeks' duration are not uncommon Bleeding may be mild and may consist chiefly of purpura petechiæ and slight bleeding from the gums or it may be extremely severe and necessitate repeated transfusions Cerebral hemorrhage is not uncommon during or shortly following exacerbations The patient may be admitted to the hospital after an apoplectic stroke A few cases have been described in which subcutaneous hematoma is a prominent feature and it has been suspected that some of the cases of essential hematuria may be due to hemorrhagic purpura

There is no family history of hemorrhagic disease, such as there is with hemophilia Changes in the joints are not common, although occasionally milder forms of infectious arthritis have been described with hemorrhagic purpura In contradistinction to acute aplastic anemia the history of bleeding antedates the development of anemia whereas in acute aplastic anemia hemorrhage is a secondary development An acute case may be very difficult to distinguish

from a case of acute aplastic anemia here one must rely chiefly on evidence of normal regeneration of the blood which is present in hemorrhagic purpura Hemorrhagic features of leukemia may be similar to those of hemorrhagic purpura but morphologic study of blood smears reveals immature cells

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TABLE I

FEATURES OF COAGULATION IN HEMORRHAGIC DISEASES. DIFFERENTIAL DIAGNOSIS*

Characteristics	*Hemophilia*	*Purpura hemorrhagica*	*Aplastic anemia*	*Acute leukemia*
Leukocyte count, total	Normal	Increased or normal	*Progressively decreased*	Normal, increased or decreased
Leukocyte count, differential	Normal	Normal distribution, normal cells	*Relative lymphocytosis*	*Immature cells, especially stem cells*
Signs of regeneration of erythrocytes	Normal	Reticulocyte count usually increased, polychromatophilia and anisocytosis	*Reticulocyte count low, polychromatophilia and anisocytosis usually absent*	Usually normal
Platelet count	Normal	*Decreased*	Decreased	Increased, normal or decreased
Bleeding time	Normal or slightly prolonged	*Prolonged*	Prolonged	Normal or prolonged
Coagulation time, venous blood	*Prolonged*	Normal	Normal or prolonged	Normal or prolonged
Retractility of clot	Normal, reclotting phenomenon	*Delayed or absent*	Normal, delayed or absent	Normal, delayed or absent
Prothrombin time	Prolonged	Normal or prolonged	Normal or prolonged	May be prolonged
Tourniquet test	Negative	Usually positive	Frequently positive	May be positive
Heredity	Positive, occurs in males, transmitted by females	Little significance	No significance	No significance
Joint hemorrhages	Common	Rare	Rare	Rare
Petechia and purpura	Rare	Common	Common	Not uncommon

* Important features are italicized. The results of laboratory tests vary with the phases of the disease; at times results of certain tests may be within normal range. In infectious purpura and Henoch's purpura the results of laboratory examination are indefinite and frequently within normal range.

philia anisocytosis with predominance of macrocytes occasional normoblasts and absence of a decided shift to the right of polymorphonuclear cells argue against the presence of an aplastic marrow and indicate that splenectomy will be followed by a satisfactory result Hemorrhagic disease due to chemical poisoning may or may not show indications of aplastic marrow and the patients should be treated medically some of the patients will recover and some will not Occasional cases of hemorrhagic disease have been reported which could not be properly classified These were cases with normal platelet counts but with other features of hemorrhagic purpura cases with a history of familial bleeding but which do not conform to hemophilia and cases with features of hemorrhagic purpura but in addition an enormous increase in the viscosity of the blood apparently as a result of abnormalities of the serum proteins These unusual types of hemorrhagic disease cannot at present be regarded as suitable for splenectomy

Treatment — Radical changes in the treatment of hemorrhagic purpura have occurred in recent years as a result of the demonstration of the remarkably beneficial effect of splenectomy Experience seems to indicate that unfavorable results following splenectomy have been due chiefly to inaccurate diagnosis and to failure to eliminate focal infection after splenectomy Patients with acute aplastic anemia and acute leukemia have been operated on under the misapprehension that they had hemorrhagic purpura It has been demonstrated recently that even in acute cases when a satisfactory diagnosis of hemorrhagic purpura can be made and when acute aplastic anemia acute leukemia and acute hemorrhagic disease secondary to chemical poisoning can be excluded symptomatic cure can be effected by splenectomy Mild recurrences have occurred in some of the cases after splenectomy but in my experience these have ceased when focal infection in tonsils and teeth has been eliminated In one case it was necessary to use radium for small bleeding fibromyomas Transfusions have been required in some cases to carry the patient through the period of postoperative readjustment

From March 7 1923 to January 1 1931 41 patients with hemorrhagic purpura were subjected to splenectomy at the Mayo Clinic Two patients died in hospital one of whom was admitted with symptoms of incipient cerebral hemorrhage and an emergency operation was performed in the hope of preventing extension Thirty nine of the patients are living of whom 36 are in satisfactory health 4 are living seven years after operation 9 more than six years and 2 more than four years

Surgical procrastination is difficult to overcome in this disease even after definite diagnosis and the fear of hemorrhage at operation in the more severe cases still lingers in spite of demonstrations that it is not a hazard A definite diagnosis of hemorrhagic purpura whether of chronic remittent type or of sub-

acute or acute type, means a decision for splenectomy If possible, the erythrocyte count should be brought to 2,500 000 cells in each cubic millimeter of blood by transfusions but if the blood count is forced too high, or if surgical treatment is postponed cerebral hemorrhage may occur Coagulants are of little value a coagulant containing platelet extract may be tried Irradiation of the spleen has been temporarily effective in reducing the amount of bleeding Large doses of iron may be given and a blood building type of diet is essential Curettage for uterine hemorrhage has been employed with improvement in some cases but is not justifiable as a substitute for splenectomy in view of the low operative mortality of splenectomy Tamponage may be necessary for severe nasal or uterine bleeding while the patient is being treated for severe anemia Gastrointestinal hemorrhage requires the usual regimen and treatment Transfusions may be given either by the direct method or the citrate method, both are temporarily effective Improvement on medical measures however, should not lead to procrastination with respect to surgical treatment except possibly in mild cases of short duration For cases of indeterminate hemorrhagic disease splenectomy is not at present advisable

Myelogenous Leukemia

This condition is considered in chapter XVII of volume 2 Chronic types of leukemia, as well as true aleukemic leukemia by the latter of which terms I mean leukemia which cannot be demonstrated in life by morphologically abnormal forms in the blood may at times give great difficulty in diagnosis During remissions patients with chronic leukemia may present normal blood pictures, and to distinguish this condition from other forms of splenomegaly particularly from splenic anemia sometimes requires prolonged observation The situation is confused also by the fact that even after prolonged study suspicion of leukemia may not be aroused, and a typical blood picture may appear only after splenectomy Moreover it is possible that a patient may suffer from the clinical syndrome of splenic anemia for years and leukemia may develop later Fortunately in such cases even after splenectomy has been performed, the expectancy of life of the patient is not less than that which accompanies the disease in general and the patient may even be benefited by the procedure Great care must be exercised also to recognize acute leukemia when leukopenia with hemorrhagic features is present otherwise splenectomy may be advised on the basis of a mistaken diagnosis of hemorrhagic purpura Acute leukemia may be confused also with acute aplastic anemia the latter of which is considered elsewhere

The spleen of chronic myelogenous leukemia may be of any size often it is very large On the other hand a diagnosis is not infrequently made from ex

amination of the blood when the spleen cannot be felt The splenic pulp and venous sinuses are enormously engorged with all varieties of myeloid cells the splenic nodules are obliterated, and varying degrees of myeloid metaplasia and fibrosis are present

Forty six patients with chronic myelogenous leukemia were submitted to splenectomy at the Mayo Clinic chiefly between the years of 1916 and 1925 Preliminary treatment by radiotherapy was carried out and improvement of the general condition of the patients was brought about by medical measures There were 3 deaths in hospital a mortality of less than 7 per cent Forty three patients have been traced and of these 41 have died Two are living and are in fairly good health respectively three years and four and a half years after operation

The patients felt better after splenectomy were less anemic and less toxic, and recurrences were less frequent Life was not materially if at all longer than the general expectancy of patients with the disease and final deterioration at the end of from two to six years was very rapid Splenectomy might be advised for a young patient with a chronic type of myelogenous leukemia or early in the course of the disease even so it would be difficult to justify the risk and discomfort of a major operation

Lymphatic Leukemia

This disease is considered in chapter XVII of volume 2 Occasionally a case of lymphatic leukemia may be seen in which the spleen is considerably enlarged and lymph nodes elsewhere in the body cannot be palpated Usually the diagnosis can be made easily by examination of the blood Sometimes however when definite immaturity cannot be found and the percentage of lymphocytes is not exceedingly high a distinction from splenic anemia lymphosarcoma and Hodgkin s disease may be impossible Acute lymphatic leukemia may be confused with agranulocytosis and acute infectious mononucleosis

The spleen undergoes extreme lymphoid hyperplasia with varying degrees of fibrosis Splenectomy has not been performed in a sufficient number of cases of chronic lymphatic leukemia for its value to be known

Monocytic Leukemia

Monocytic leukemia may be regarded as a form of reticulo-endotheliosis The spleen is not much enlarged but there is marked proliferation of mononuclear cells that probably are derived from undifferentiated reticular cells In advanced stages of the disease not only a high percentage of monocytes but also histiocytes may be found in the circulating blood More than thirty cases

of this disease have been reported, and it has now become a well recognized third type of leukemia

Chloroma

Choloroma is a form of leukemia with subperiosteal infiltration of the bones chiefly of the flat bones of the skull and infiltration of nerves, glandular structures and other tissues the tumors are often green The spleen may be enlarged especially in the myelogenous type Chloroma is considered also in chapter XVII of volume 2

Lymphosarcoma and Hodgkin's Disease

Other sections to be consulted concerning these conditions are as follows chapter I of volume 4 chapter XVII of volume 2 and chapter XIX–A of volume 5 Rarely Hodgkin s disease in its early stages is confined chiefly to the spleen One such case in which splenectomy was performed, was seen at the Mayo Clinic The patient died within a year with symptoms indicative of involvement of retroperitoneal structures Other forms of lymphosarcoma may be difficult to distinguish from Hodgkin s disease even on pathologic examination of tissue, and they also merge into more malignant types of sarcoma Spleens of 7 patients in my experience gave evidence of marked lymphocytic hyperplasia without evidence of leukemia Of these one patient was living in good health thirteen years after operation when last heard from in 1920 and one is living in good health eleven years after operation In both of these cases marked increase of lymphoid tissue was observed in the latter lymphocytic infiltration was also present in tissue removed from the liver but a diagnosis of malignant lymphosarcoma could not be made It is impossible at present to arrive at an accurate conception of the fundamental relationships in this group of diseases or to evaluate the effect of splenectomy

Eosinophilic Hyperleukocytosis with Splenomegaly

A few cases of marked splenomegaly associated with persistent leukocytosis and extreme eosinophilia have been reported in the literature The percentage of eosinophils may be as high as 80 or 90 In some of the cases hyperplastic pleurisy perihepatitis and perisplenitis have been present The bone marrow lymph nodes and spleen have been found to be engorged with eosinophils Some of these cases have been reported as cases of eosinophilic leukemia but although myelocytes have been found in the blood and tissues extreme immaturity has not been demonstrated This eosinophilia may be due to the re

action of a given patient to a certain type of chronic infection Splenectomy was performed in one case of this type in my experience the patient died four years subsequently from pneumonia with empyema I have seen two other cases in which splenectomy was not advised

Pernicious Anemia

Pernicious anemia is considered in detail in chapter XVI of volume The spleen usually is palpable at some time during the course of pernicious anemia Occasionally it may be considerably enlarged The splenomegaly is clearly of a secondary nature and does not demand attention Striking changes are not present in the spleen Moderate congestion of the pulp with slight fibrosis is present many phagocytic cells containing debris are found and there is increased deposition of iron pigment

The efficacy of administration of liver liver extract hog stomach and ventriculin (an anti anemic substance derived from stomach tissue) precludes further consideration of splenectomy for this disease During the empiric stage of the treatment of this disease splenectomy was done frequently In the experience at the Mayo Clinic 6 patients were operated on in the course of the years from 1910 to 19 5 and of this series of patients only one is living at present Remission frequently occurred after splenectomy and it has not yet been determined whether or not pernicious anemia is more easily controlled by specific treatment after splenectomy At present however splenectomy does not have a place in the treatment of pernicious anemia

Acute Aplastic Anemia

This condition is considered in chapter XVI of volume 2 The spleen may be slightly enlarged in cases of acute aplastic anemia and difficulty may be experienced in distinguishing this disease from hemorrhagic purpura acute leukemia and aplastic anemia secondary to chemical poisoning The absence of evidence of normal regeneration in the blood count and in morphologic study of blood smears is the fundamental consideration in diagnosis Differential diagnosis is considered in detail in the preceding section on hemorrhagic purpura Because of the contention of some observers that hemorrhagic purpura and acute aplastic anemia are expressions of the same cause splenectomy has been done on an empiric basis In my experience three patients were submitted to splenectomy, but a favorable effect was not noted and in spite of the treatment the patients died respectively one two and three months following the operation Splenectomy is definitely contra indicated if a conclusive diagnosis of acute aplastic anemia can be made

of this disease have been reported, and it has now become a well recognized third type of leukemia

CHLOROMA

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LYMPHOSARCOMA AND HODGKIN'S DISEASE

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given three times a day for several days with close watch for excessive hemolysis in which event prompt withdrawal is necessary A considerable amount of exercise and an increased intake of fluid are important during administration of the drug Its action is cumulative and continues for ten days or more following withdrawal After the initial course of treatment the patient usually is able to remain free from symptoms with from 0 1 gm to 0 3 gm a week and he is an excellent judge of the dosage which is best for his own case

It is not possible to see at present any logical reason for splenectomy in cases of polycythemia vera it may be warranted in cases in which there is severe recurring gastro intestinal hemorrhage About 10 cases have been reported since the first operation by Cominotti in 1900 In my experience there have been three one patient died in hospital one died with tuberculosis eight years after operation and one is living four years after operation The second patient mentioned was operated on for severe recurrent gastro-intestional hemorrhage He was able to work regularly although moderately, for eight years following operation there was no recurrence of gastro-intestinal bleeding the erythrocyte count never became excessively high the leukocyte count remained in the neighborhood of 150 000 in each cubic millimeter of blood and the platelets numbered as many as 3 000 000 in each cubic millimeter of blood but the blood never presented clear-cut morphologic characteristics of leukemia The third patient reports that she is in very satisfactory health four years after operation her headaches are much improved and she is working regularly but examinations of the blood have not been obtainable

Sickle-cell Anemia

Sickle-cell anemia is also considered in chapter XXIII of volume The tendency of the erythrocytes to assume the contour of sickle cells in fresh wet preparations has been definitely shown to be hereditary congenital and familial and possibly to be confined to the blood of negroes lately it has been described as occurring in persons of the white races but the possibility of admixture of negro blood has not been excluded in all of these cases Sickle cells have been demonstrated in the blood of many negroes who are apparently in normal health they were found in 7 5 per cent of 400 negroes in Detroit Occasionally anemia develops and this may be associated with considerable or marked enlargement of the spleen and symptoms of atypical hemolytic icterus The fragility of the erythrocytes as determined by hypotonic salt solution has not however been increased Leukocytosis usually is present and a few immature leukocytes may be found in the blood smears The occurrence of ulcers of the legs may be confusing in the diagnosis

Pathologically the spleen presents a peculiar picture Extravasation of blood

POLYCYTHEMIA VERA

For further relevant material chapter XVIII of volume 2 should be consulted. Occasionally a case of true polycythemia is seen in which the spleen is not palpable usually it is moderately enlarged Patients with polycythemia vera not infrequently have been believed to be victims of neurosis at their first visit to the physician because of vague nervous manifestations exhaustion headache and vertigo In every case in which the chief complaint is pain in the legs or feet, polycythemia vera must be excluded as a possible cause Patients with polycythemia may also be seen at a time when the blood picture is normal or even when moderate anemia is present anemia may be the result of gastrointestinal bleeding Care must then be exercised in order not to classify the case as one of splenic anemia the history of features indicating preceding polycythemia may be valuable The finding of increased volume of blood with increased volume of erythrocytes will then be important evidence On the other hand advanced cases may present features such as choked disk and severe headache which may be interpreted as indicative of intracranial pressure In cases of relative or secondary polycythemia blood volume and cell volume usually are only slightly more than normal and the spleen rarely is palpable Stenosis of the pulmonary artery asthma emphysema chronic bronchitis chronic pulmonary fibrosis and cardiac disease are common primary conditions which may be associated with relative polycythemia

Splenomegaly cannot be regarded as a fundamental pathologic change in this disease a disturbance of the normal balance between production of blood and destruction of blood, with hyperplastic marrow, is present The splenomegaly is most likely to be the result of distention and an attempt to compensate for increased blood volume The spleen is engorged and fibrotic, and active phagocytosis is demonstrable Venous thrombosis in any part of the body i found frequently indefinite severe abdominal symptoms are almost always indicative of portal thrombosis

In the treatment of polycythemia vera venesection, radiotherapy and the administration of phenylhydrazine are the most effective measures Venesection gives temporary relief in nearly all cases Radiotherapy, either by means of radium or roentgen rays if it can be carried out conveniently and consistently may bring about inhibition of production of erythrocytes From a practical standpoint administration of phenylhydrazine has been more satisfactory phenylhydrazine should be used with great caution, or not at all if patients are aged more than sixty years have arteriosclerosis advanced visceral changes are bedridden or have been troubled recently with thrombosis An initial course of daily treatment usually is necessary ro reduce the blood volume and thus bring the condition under control Phenylhydrazine hydrochloride, 0 1 gm, may b

nectomy without however apparent beneficial effect the case however seems to have been one of a septic type of hypogranulocytosis Treatment by other methods has been unsatisfactory also Taussig recently reviewed with respect to treatment more than 300 cases described in the literature In those in which no specific line of treatment was used the mortality was 75 per cent in those in which arsphenamine was employed 77 per cent in those in which treatment was by transfusion 65 per cent, and in those in which roentgen therapy was instituted 55 per cent.

Perisplenitis

In perisplenitis a fibrinous exudate may appear and may lead to extreme degrees of hyperplastic proliferation of the capsule with hyaline change the result may be the so called sugar icing spleen and even calcification Tuberculosis is seen rarely in perisplenitis except as a secondary manifestation

Pain in the region of the spleen is a common complaint indeed it may be the chief complaint in most diseases associated with splenomegaly and is doubtless due to perisplenitis The history of pain may precede the history of enlargement of the spleen and not infrequently a friction rub may be heard and fremitus recognized on palpation If the friction rub of perisplenitis is heard over an abdominal tumor which is suspected to be an ectopic spleen the sign may assist in the diagnosis When perisplenitis is of extreme grade and leads to attachments to the diaphragm the risk of splenectomy is increased Following extended radiotherapy perisplenic adhesions seem to become more dense Even when the spleen is not enlarged perisplenitis may occur and cause a considerable degree of discomfort Strapping the side with adhesive tape gives partial relief and prevents aggravation of the condition

Acute Infectious Splenitis

Acute infectious splenitis is considered elsewhere in this system under the various diseases in which it occurs It is full blown in acute malaria and typhoid fever and although the spleen is not always palpable acute splenitis is frequently present in other acute exanthemata and in infection by the pneumococcus streptococcus staphylococcus and meningococcus It is described in association with typhus fever relapsing fever Malta fever and trench fever The acute splenomegaly of typhoid fever and malaria is in reality intense acute splenitis the pulp is very soft and congested and the capsule tense the splenic pulp is engorged with erythrocytes and phagocytosis by reticular cells may be active Central necrosis of the splenic nodules is present Less extreme degrees of acute splenitis in which the organ is dusky red may be seen Acute splenitis

into the tissues about the splenic nodules and venous sinuses and generalized dilatation and distortion of the capillary bed are described Sickle cells may be found in the spleen In the course of the disease, after enlargement, the spleen may become atrophic and fibrotic

Splenectomy has been reported in the literature as having been applied in approximately 10 cases The results have not been definite more favorable results may have been obtained in cases in which the spleens have been larger but the results are not uniformly satisfactory as they are in hemolytic icterus Splenectomy has no influence on the sicklemia

Agranulocytic Angina

In chapter XXII of volume 2 agranulocytic angina is also considered Since the report of Schultz in 1922 agranulocytic angina has become an important clinical entity It was described first however by Brown Agranulocytosis and hypogranulocytosis are seen not only as the syndrome agranulocytic angina, but also as a result of infection radiotherapy, administration of benzol of preparations of arsenic and especially of the various types of arsphenamine In all of these conditions there is either well marked reduction or complete absence of granulocytes in the circulating blood and all grades of severity have been reported The percentage of lymphocytes is relatively increased, but frequently the absolute count is much less than normal Leukopenia often is of extreme degree Necrotic ulceration in the mouth, pharynx, or vagina, on the vulva about the rectum on the perineum or buttocks and in various parts of the gastro intestinal tract is common Cases of agranulocytosis and hypogranulocytosis must be distinguished from cases of acute leukemia acute aplastic anemia hemorrhagic purpura subacute bacterial endocarditis, cancrum oris and acute poisoning especially by arsenical preparations and benzol Complete or nearly complete agranulocytosis whether secondary or a part of the syndrome of agranulocytic angina carries a very serious prognosis At least two-thirds of the cases reported ended in death

The spleen may or may not be palpable in cases of agranulocytosis and hypogranulocytosis It is usually however not very much enlarged Increase in the number of reticular cells in the spleen lymph nodes and bone marrow with absence of granular leukocytes has been reported There is also absence of granular leukocytes in the necrotic ulcers

On theoretic consideration in view of the polymorphonuclear leukocytosis which occurs after experimental splenectomy and after splenectomy in man for various conditions it might be suspected that splenectomy in this condition would be beneficial possibly by removing some inhibition to the activity of the bone marrow On this basis Balridge submitted one of his patients to sple

endarteritis with thrombosis Embolus usually arises from lesions of the left side of the heart Infarction involving the entire organ as a result of embolus of the splenic artery or of thrombosis of the vessels of the pedicle following torsion has been described also but it is rare Small infarctions are found frequently at postmortem examination and occur in all diseases associated with splenomegaly They are especially common however in subacute bacterial endocarditis polycythemia vera splenic anemia and chronic infectiou splenomegaly Infarction usually proceeds to formation of scar tissue but abscess or cyst may result Clinically a fairly accurate diagnosis of splenic infarction can be made in the presence of any of the diseases in which infarction is likely to occur when acute pain has been experienced in the splenic region perisplenic friction may be heard Treatment is directed toward relief of symptoms strapping the side with adhesive tape may prevent irritation Sometimes narcotics and supportive measures are necessary

Amyloid Spleen

Amyloid spleen once commonly found when many cases of chronic suppurative disease existed is now rarely to be considered in the differential diagnosis of splenomegaly It can be suspected following years of chronic suppurative disease it may be associated with the suppurative processes of tuberculosis and syphilis Amyloid degeneration has been described in two forms the sago spleen in which most of the amyloid material has been deposited about the splenic nodules and the waxy spleen in which the amyloid infiltrates the pulp Congo red injected intravenously is of diagnostic aid in amyloid disease since it disappears from the blood stream very rapidly when amyloid infiltrates the tissues The splenomegaly is a secondary condition and does not demand independent treatment

Tuberculous Splenomegaly

Tuberculosis is considered in detail in chapter XII of volume 5 Occasionally tuberculosis i largely localized to the spleen and produces marked splenomegaly with anemia although the primary lesion was doubtless originally elsewhere in the body Localized splenic tuberculosis may be suspected clinically when a satisfactory history of former tuberculous peritonitis can be obtained and when calcified tubercles can be demonstrated in the spleen roentgenologically However, the condition usually has been recognized only on pathologic examination of the surgically removed spleen or at postmortem examination Tuberculosis may be found in other types of splenomegaly and in these cases it is explained most logically as a coincidental condition It is es

usually subsides, but rupture may occur on slight trauma rarely, infiltration of polymorphonuclear cells may become extreme, resulting either in multiple miliary abscesses a large single abscess or complete suppuration of the entire spleen

Subacute Infectious Splenomegaly

Subacute infectious splenomegaly occurs in the more chronic types of bacteremia and in undulant fever and tularemia

Splenectomy has been reported as having been performed in a few cases of subacute infection associated with definite splenomegaly, but it has not favorably affected the course of the disease Two such cases have occurred in my experience with subsequent death in each instance, two months after operation The spleen contained small multiple abscesses

Abscess of the Spleen

Abscess of the spleen may be difficult of diagnosis, and to distinguish it from perinephric and subphrenic abscess may be impossible Abscess of the spleen usually is metastatic in origin but may occur following trauma metastatic abscesses are likely to be multiple Abscess also is not infrequent in association with carcinoma of the neighboring organs and has been described following acute suppurative appendicitis Clinically the condition is suspected when evidence of inflammatory reaction is localized to the region of the spleen, and intermittent fever and other evidences of infection are present After reasonable means of exclusion of other conditions have been employed exploratory operation is advisable and surgical treatment without unnecessary delay is best Preliminary exploratory aspiration is warranted but even if the results are positive surgical exploration may be necessary Splenectomy must be reserved for the cases in which the spleen can be easily removed In other cases the type of surgical procedure must be adapted to the conditions found at exploration Drainage has been effected most frequently by a lateral stab wound In some instances it is advisable to perform the operation in two stages, penetrating the pleura and walling off the pleural cavity at the first operation At the Mayo Clinic splenectomy has not been performed primarily for splenic abscess in any case but in several cases drainage has been done for abscess secondary to other conditions

Infarction

Infarction of the spleen may be the result of embolus or may arise in situ The arteries of the spleen are end arteries and therefore, are more susceptible to

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pecially common in association with polycythemia vera I have found in the records of the Mayo Clinic instances of inactive miliary tuberculosis of the spleen in association with hemorrhagic purpura, hemolytic icterus splenic anemia and myelogenous leukemia

Leprosy

The main consideration of leprosy is in chapter XIII of volume 5 There is practically always marked nodular infiltration of the spleen in leprosy, and organisms of leprosy can be demonstrated in the organ I do not know of any reports of splenectomy in leprosy

Mycosis

Mycotic infection is considered in chapter XIV of volume 5 Lesions of the spleen are common in cases of actinomycosis, streptothricosis blastomycosis coccidioidal granuloma sporotrichosis and other rarer forms of mycotic disease In actinomycosis the spleen is likely to be enlarged in severe cases In chronic types of mycotic disease and secondary infection the spleen may become very much enlarged but splenectomy has not played a part in the treatment

Considerable confusion exists by reason of the discussion in the literature concerning Gandy bodies and nodular siderosis This particular condition has been described by McNee from the pathologic standpoint, as splenomegaly with peri ellipsoidal hemorrhage and nodular siderosis Nodular siderosis apparently occurs in a variety of clinical types of splenomegaly It is believed by some investigators that it is due to mycotic infection but the evidence seems to indicate that in most if not all of the cases in which this condition is found the histologic changes may be explained by deposition of iron pigment in elastic fibers Nodular siderosis is considered in this chapter in the section on pathology

Glanders

Glanders is considered in chapter VIII of volume 5 The lesions of glanders in the spleen may be small multiple foci with necrotic centers or larger abscesses In chronic cases the lesions may heal with considerable fibrosis

Beri beri

A consideration of beri beri is to be found in chapter XII of volume 4 Very slight splenomegaly sometimes occurs with beri beri it is not a prominent feature

Ectopic and Movable Spleen

Occasionally abdominal exploration is performed for pelvic tumor and the tumor proves to be an enlarged ectopic spleen Even those especially interested in diseases of the spleen have made this mistake Occasionally a case is seen in which there is a very movable moderately enlarged spleen which on account of elongation of its pedicle can be moved to different parts of the abdominal cavity or the spleen may be fixed in an abnormal position Torsion of such a movable spleen also occurs and acute symptoms develop

An ectopic and movable spleen usually can be suspected by its contour by palpation of its edge or notch and sometimes by demonstration of the friction rub of perisplenitis by auscultation Absence of the spleen from its usual position may be suspected from the results of palpation percussion or roentgenography

A movable spleen whether enlarged or not should be regarded as a menace and splenectomy should be advised Moreover it may not be possible to arrive at an absolute diagnosis and exploration may be necessary Acute torsion of the pedicle demands immediate surgical treatment I have observed two cases in which splenectomy has been performed for this condition Both patients are alive and well respectively twenty three years and nineteen years following splenectomy

Aneurysm of the Splenic Artery

Although rare aneurysm of the splenic artery is a condition which should at least be kept in mind by the internist because of its importance and because it is likely to be associated with moderate enlargement of the spleen Attacks of pain in the upper part of the abdomen have been described as rather commonly present and some of these attacks have been associated with syncope Rarely a separate mass has been palpable in which pulsation and thrill have been recognizable In a suspected case that was under my observation the bruit was heard best in the back near the spinal column Arteriovenous aneurysm of the splenic vessel also has been described If aneurysm of the splenic artery is suspected exploratory operation should be performed with a view to excision of the aneurysm and of the spleen

Cysts

Cysts of the spleen may be parasitic or nonparasitic Echinococcus disease is the outstanding parasitic condition Echinococcus disease of the liver is considered in chapter VI of volume 3 and in chapter XXXIX of volume 5

In certain parts of the world, notably Australia and New Zealand the primary consideration in the diagnosis of any abdominal tumor is exclusion of echinococcus disease the disease is not uncommon in North America Although the spleen does not seem to be commonly involved, nevertheless splenic tumor due to hydatid disease may occur, and when echinococcus disease involves the liver, splenomegaly may be present Hydatid of the left lobe of the liver may present a problem in differential diagnosis Both the complement fixation test of the blood and the cutaneous sensitization test have proved to be very valuable provided a satisfactory antigen can be obtained Diagnosis is confirmed only by exploratory operation and evacuation of cysts Puncture of the cyst prior to operation for diagnostic purposes may be a dangerous procedure if the fluid from the cyst escapes into the peritoneal cavity

Of nonparasitic conditions small multiple cysts of the capsule, up to 1 cm in diameter and situated chiefly in the hilum or near the notch, are commonly found at postmortem examination These are probably lymphatic cysts Small multiple or single, large cysts of the substance of the spleen may occur, Large serous cysts are not common Cysts may result also from infarct Large hemorrhagic cysts are seen occasionally some of them probably secondary to trauma or to serous cyst, but others are idiopathic Dermoid cyst has been reported Polycystic disease of the spleen with splenomegaly and enlargement of the liver is suspected when bilateral enlargement of the kidneys can be demonstrated and when the diagnosis of polycystic renal disease can be confirmed by cystoscopy or intravenous urography

In the experience at the Mayo Clinic hemorrhagic cyst was found at exploratory operation in two cases Splenectomy was done in both and one patient is living in good health nine years after operation the other died eight months later with empyema In a large series of cases in which splenectomy has been done I have not seen a case of large serous cyst or of dermoid cyst, small cysts have been reported at operation for other conditions

Tumors

Primary carcinoma of the spleen has been definitely proved not to occur and secondary metastatic carcinoma is rare The spleen both experimentally and from a clinical standpoint seems to possess resistance to the development of carcinoma and sarcoma Occasional cases of sarcoma of the spleen have been described in which the sarcoma was of the type of lymphosarcoma fibrosarcoma or endothelial sarcoma apparently primary in the spleen and when seen limited to that organ Angiomatous tumors some of them with large cavernous sinuses are not exceedingly rare

In the experience at the Mayo Clinic one patient with malignant endothelial

sarcoma of the spleen is living in good health four months following splenectomy. The spleen in this case contained numerous nodules of variable size; the weight was 2975 gm. Tissue was excised at exploratory operation in two cases of fibrosarcoma of the spleen but splenectomy was not done. There was also one case of hemangioma of the spleen with subsequent death of the patient.

Rupture

Splenic rupture is of especial interest to the diagnostician not only because the condition constitutes an emergency but also because of the necessity following minor injuries to the spleen of recognizing the symptoms of impending secondary rupture following a latent period. Rupture of the spleen may be either spontaneous or traumatic. Spontaneous rupture has been reported in malaria, leukemia, typhoid fever, typhus fever, ulcerative endocarditis and hemorrhagic purpura. There is reason to think that most of the cases of so-called spontaneous rupture of the normal spleen reported in the literature were in reality cases of secondary rupture resulting from former injury and separated from it by a latent period. The recognition of traumatic rupture ordinarily is not difficult. Abdominal pain and symptoms of shock following severe injury, subsequent localization to and rigidity of the muscles of the left upper abdominal quadrant with pain referred to the left shoulder present a definite picture. Severe injuries may tear the large vessels of the pedicle and hilum. In certain cases localization to the left upper quadrant has not been present, probably due to free intraperitoneal bleeding. It might be said that intraperitoneal hemorrhage found at exploration in the male is most likely to be due to ruptured spleen, in the female to ectopic gestation with rupture.

The symptoms are necessarily greatly modified by the nature of the injury and the progress of the hemorrhage. Minor injuries may consist only of splenic contusion or slight capsular rupture in which the symptoms and signs are very slight. Intrasplenic hematoma and subcapsular hemorrhage may occur without capsular rupture. In these the initial symptoms are also likely to be mild and of only a few hours duration. Perisplenic hematoma may be controlled by the omentum and by self limitation, or gradual oozing into the abdominal cavity may occur with gradual deterioration of the patient, progressive anemia and indefinite abdominal symptoms.

Minor injuries may be followed by complete absorption of the hematoma with formation of cysts or with the formation of a whitish fibrous tumor. Subcapsular hemorrhages may gradually extend, separating capsule from splenic tissue, to be followed later by secondary rupture caused by very slight increase of intrasplenic pressure. Under these circumstances the spleen may almost explode and be torn into many fragments.

In certain parts of the world, notably Australia and New Zealand, the primary consideration in the diagnosis of any abdominal tumor is exclusion of echinococcus disease the disease is not uncommon in North America Although the spleen does not seem to be commonly involved, nevertheless splenic tumor due to hydatid disease may occur, and when echinococcus disease involves the liver, splenomegaly may be present Hydatid of the left lobe of the liver may present a problem in differential diagnosis Both the complement fixation test of the blood and the cutaneous sensitization test have proved to be very valuable provided a satisfactory antigen can be obtained Diagnosis is confirmed only by exploratory operation and evacuation of cysts Puncture of the cyst prior to operation for diagnostic purposes may be a dangerous procedure if the fluid from the cyst escapes into the peritoneal cavity

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In the experience at the Mayo Clinic one patient with malignant endothelial

ture The usual measures for shock and loss of blood will be necessary before and after operation

Outline of Diagnostic Features of Diseases of the Spleen

Hemolytic Icterus —A familial history is common Jaundice is of the acholuric type There is increased fragility of erythrocytes microcytosis with spherical erythrocytes and an increased percentage of reticulated erythrocytes Some patients do not have jaundice when they come under observation Splenomegaly in association with biliary colic is likely to be due to hemolytic icterus The hemolytic type of jaundice is seen also in diseases other than hemolytic icterus especially in cirrhosis of the liver sickle-cell anemia and chemical poisoning chiefly by phenylhydrazine and benzol Carotinemia produces an appearance of jaundice

Potential Splenic Anemia —Marked splenomegaly without anemia is the basis of such a diagnosis when all oth r possible causes of splenomegaly have been excluded

Splenic Anemia —Primary splenomegaly secondary anemia and frequently a history of gastro intestinal hemorrhage are present In the later stages marked cirrhosis of the liver and portal thrombophlebitis and thrombosis may exist The diagnosis is made by exclusion of other causes of marked splenomegaly chiefly hemolytic icterus chronic infectious splenomegaly malarial splenomegaly cirrhosis of the liver syphilitic splenomegaly primary portal thrombophlebitis polycythemia vera Gaucher s disease marble bone disease sarcoma the various forms of leukemia tropical splenomegaly and other uncommon diseases In some cases cirrhosis of the liver and splenitis advance concomitantly

Chronic Infectious Splenomegaly —The clinical syndrome may be that of splenic anemia Splenomegaly develops as a result of chronic recurring infectious processes (exclusive of tuberculosis syphilis and malaria) There may be a history of one of the following diseases tonsillitis arthritis phlebitis endocarditis furunculosis portal thrombophlebitis or ulcerative colitis

Primary Portal Thrombophlebitis —This condition is properly grouped with chronic infectious splenomegaly Other causes of splenomegaly are excluded as in splenic anemia There is a history of recurrent periods of illness characterized by abdominal distention and pain without localization with fever and chills over a period of years with the development of splenomegaly and frequently a history of splenic infarcts Portal thrombosis occurs early with this condition but late with many other types of splenomegaly

Cirrhosis of Liver —Evidence of hepatic disease precedes the history of splenomegaly The spleen usually is not as large as that of primary splenomeg

In about half of the cases the original injuries have been mild. Even falling out of bed has been known to cause subcapsular hemorrhage with secondary rupture after a latent period. Secondary rupture frequently has been caused by coughing, sneezing and lifting; indeed an apparent cause has not been elicited in many cases.

It is most important, from the diagnostic standpoint, to recognize the latent period following suspected injury of the spleen which so frequently culminates in fulminating and fatal secondary hemorrhage. This latent period may be of short or of very long duration. It is usually from two to nine days, but occasional cases have been reported in which it has been so long as six months. The patient may recover rather promptly from the original injury and resume his activities. It has been demonstrated, however, that in almost all of the cases certain symptoms and signs are likely to be present during the latent period. The patient may complain of a persistent, dull ache in the left side with occasional lancinating pain. Rigidity of the muscles of the left upper abdominal quadrant usually can be demonstrated, and there may be an increase in the splenic dulness and a doughy, indefinite sense of enlargement at the left costal margin. Elevation of the left half of the diaphragm may be demonstrated roentgenologically and pain may be reflected to the region of the left shoulder through the phrenic nerve and the third and fourth cervical segments. Hemoglobin and erythrocyte count may be low, and persistent leukocytosis is likely to be present. Consequently, a patient who has received an injury over the splenic region or who has sustained fracture of the ribs of the left lower part of the thorax, should be kept at rest and watched carefully for symptoms indicative of perisplenic or of subcapsular hematoma. In view of the relatively high mortality reported as a result of secondary hemorrhage, exploratory operation should be seriously considered during the latent period if persistence of the symptoms is satisfactorily demonstrated.

Treatment. — In a few cases an attempt has been made to pack the splenic wound; however the treatment of choice is prompt splenectomy. It would seem that the operative mortality of traumatic rupture of the spleen in general has been too high, more than 5 per cent, in the reported cases. This mortality should be considerably reduced by prompt exploration and splenectomy in severe cases, by careful expectant treatment of minor injuries to the spleen, by recognition of symptoms in the latent period and possibly by splenectomy in the latent period before secondary rupture. Concomitant rupture of the gastrointestinal tract is a serious complication in severe injuries. Of six patients seen at the Mayo Clinic two died within a day of operation; in one of these cases rupture of the stomach was present and in the other rupture of the duodenum. The remaining four patients are living and well, two of whom had delayed rup-

to the fetal type of hematopoiesis may explain the blood picture Von Jaksch s syndrome may be a secondary manifestation or a precursor to splenic anemia of the adult type

Rickets and Scurvy — Splenomegaly is a secondary manifestation

Hemorrhagic Purpura — Differential diagnosis is necessary to a decision for splenectomy The spleen may be slightly or moderately enlarged There are acute subacute and chronic recurring types The following characteristics are seen low platelet level long bleeding time delayed retractility of clot and evidence of active regeneration of blood Bleeding precedes the development of anemia Hemophilia is to be distinguished by its long coagulation time family history and involvement of joints acute leukemia by immaturity of leukocytes especially when leukopenia is present and acute aplastic anemia by evidence in the blood of markedly decreased regeneration and an anemia unexplained by hemorrhage Hereditary hemorrhagic telangiectasia must not be overlooked in this condition the spleen usually is not enlarged

Indeterminate Types of Hemorrhagic Disease — This is a group with various ill defined features of coagulation which are not understood. Splenectomy is contra indicated at the present time

Myelogenous Leukemia — The spleen may be small or very large Chronic cases during periods when the blood is normal may have to be distinguished from cases of splenic anemia Leukemia may develop after years of what seems to be potential splenic anemia Acute cases with leukopenia have to be distinguished from hemorrhagic purpura and acute aplastic anemia

Lymphatic Leukemia — The spleen may be very large and the lymph nodes not palpable Distinction from lymphosarcoma and Hodgkin s disease may be impossible Acute cases have to be distinguished from cases of hemorrhagic purpura acute aplastic anemia agranulocytic angina and infectious mononucleosis

Monocytic Leukemia — This is a form of reticulo-endotheliosis with a high percentage of monocytes and in advanced cases histocytes in the blood

Lymphosarcoma and Hodgkin s Disease — Splenic lymphosarcoma or splenic Hodgkin s disease has been diagnosed only on pathologic examination

Eosinophilic Hyperleukocytosis with Splenomegaly — This is a form of chronic splenomegaly with marked eosinophilia the percentage of eosinophils may be as high as 80 or 90 This is probably not a true form of leukemia but a peculiar reaction to chronic infection

Pernicious Anemia — This is rarely associated with a large spleen There are combined sclerosis glossitis achlorhydria macrocytosis of erythrocytes and shift to the right of polymorphonuclear leukocytes

Acute Aplastic Anemia — Progressive anemia and leukopenia with evidence of very inactive regeneration in the blood smears are seen The number of

aly The retention of dye on the test of hepatic function is relatively more marked and ascites is more likely to occur early There may be a history of alcoholism Some cases of cirrhosis of the liver are associated with a hemolytic type of anemia

Hemochromatosis — Cirrhosis of the liver chronic splenitis, pigmentation of the skin and glycosuria constitute the syndrome Argyria and Addison's disease must be excluded Patients may be seen before major characteristics are clearly defined

Chronic Hyperplastic Polyserositis — Splenomegaly and cirrhosis of the liver with a history of polyserositis are characteristic Pericarditis with adhesions is common

Syphilitic Splenomegaly — The Wassermann test is persistently positive There may be other evidences of syphilis and hepatic enlargement suggestive of the presence of gumma Occasionally hemolytic icterus produces a strongly positive Wassermann test a weakly positive test may occur with any severe form of anemia Syphilis may also coexist with other forms of splenomegaly

Gaucher's Disease — Splenomegaly frequently dates from childhood Two or more cases may occur in the same generation It is most common among Hebrews Osteoporosis and increase of medullary cavities are found on roentgenologic examination of the bones There are fat pads resembling pingueculæ on the sclera and pigmentation of the skin is common Biopsy of sternal marrow may reveal the typical large reticular cells

Marble Bone Disease — Splenomegaly is associated with roentgenologic indications of osteosclerosis producing very dense shadows of the bones Myeloid metaplasia of spleen liver and lymph nodes is a secondary development, severe anemia may be present with a morphologic picture somewhat suggestive of leukemia

Malarial Splenomegaly — Chronic malarial splenomegaly may simulate splenic anemia A history of recurring attacks of malaria is necessary to the diagnosis plasmodia usually are not found

Egyptian and Colombian Splenomegaly — These are either forms of splenic anemia or the result of parasitic disease after the parasites have disappeared

Kala azar — Leishman Donovan bodies are demonstrated in the leukocytes of the circulating blood in the material obtained by splenic puncture or by examination of excised lymph nodes

Schistosomiasis — Splenomegaly results from the presence of flukes in the portal vessels

Splenomegaly with Anemia in Infancy — There are many causes dietary deficiency, chronic infection syphilis rickets scurvy, hemolytic icterus sickle cell anemia erythroblastic anemia leukemia, or hemorrhagic purpura A reversion

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Cysts and Tumors — The nature of these enlargements may be suspected by their contour Sarcoma of the spleen is likely to produce an irregular tumor the history is of short duration Echinococcus can be recognized by the complement fixation test Polycystic disease may be justifiably suspected on diagnosis of bilateral polycystic renal disease

Rupture — Acute rupture is associated with generalized abdominal or localized pain evidence of loss of blood and shock It is very important to recognize the symptoms of impending secondary rupture during the latent period following minor injury Most cases of spontaneous rupture in reality are cases of secondary rupture ten days or more following a minor injury

BIBLIOGRAPHY

BELL E T A Text book of Pathology Lea and Febiger Philadelphia 1930

HIRSCHFELD HANS Die Erkrankungen der Milz J Springer Berlin 19 0

HIRSCHFELD HANS and MÜHSAM R Chirurgie der Milz F Enke Stuttgart 1930

MacCALLUM W G A Text book of Pathology Ed 4 W B Saunders Co Philadelphia 1928

MAXIMOW A A A Text book of Histology W B Saunders Co Philadelphia 1930

MOYNIHAN B G A The Spleen and Some of its Diseases W B Saunders Co Philadelphia 1921

PEARCE R M KRUMBHAAR L B and FRAZIER C H The Spleen and Anæmia J B Lippincott Co Philadelphia 1918

POOL E H and STILLMAN R G Surgery of the Spleen D Appleton and Co New York 1923

Anatomy Histology Embryology Physiology and Pathology

ASCHOFF LUDWIG Lectures on Pathology Paul B Hoeber Inc New York 19 4

ASCHOFF L and KIYONO Zur Frage der grossen Mononuclearen Folia Hæmatol 1913 XV 383

BARCROFT JOSEPH Recent knowledge of the spleen Lancet 1925 I 319

CHANEY W C Splenic anemia a clinical and pathological study of sixty nine cases Am Jour Med Sc 19 3 CLXV 856

CHRISTIAN H A Defects in membranous bones exophthalmous and diabetes insipidus an unusual syndrome of dyspituitarism Med Clin N Amer 1920 III 849 Also *Contributions to Medical and Biological Research dedicated to Sir Wm Osler* vol 1 p 390 Paul B Hoeber New York 1919

CONNER H M Blood pathology in relation to surgery Jour Lab and Clin Med 1931 XVI 647

DANTSCHAKOFF WERA Über das erste Auftreten der Blutelemente im Hühnerembryo Folia Hæmatol suppl 1907 IV 159

reticulated erythrocytes is low, and polychromatophilia is absent Hemorrhagic features similar to those of hemorrhagic purpura may develop Acute leukemia is distinguished by the immaturity of leukocytes, the demonstration of which may however require repeated examinations of the blood

Polycythemia Vera — The volume of whole blood and of erythrocytes and the viscosity of the blood are increased The blood vessels of the fundi are engorged Erythrosis is evident If the case simulates splenic anemia, estimation of blood volume is essential Gastro intestinal hemorrhage may produce temporary anemia Early cases have been diagnosed as neurosis Relative polycythemia usually is secondary to cardiac or pulmonary disease

Sickle cell Anemia — This is entirely or chiefly, confined to negro blood The erythrocytes are crescentic in wet preparations Splenomegaly and atypical hemolytic jaundice may develop Ulcers of the legs are present in some cases

Agranulocytosis — The first type is agranulocytic angina, the second, agranulocytosis and hypogranulocytosis secondary to infection or various chemical and physical agents Granular leukocytes are absent or almost absent from the circulating blood Anemia is not a prominent feature Leukopenia usually is of extreme degree Necrotic ulcers of the mouth pharynx, rectum vagina buttocks and gastro intestinal tract are a feature of agranulocytic angina

Abscess of Spleen — This is to be suspected when there is pain in the splenic region an unexplained fever and when other causes of splenomegaly have been excluded

Infarction — This is to be suspected when there is pain, localized in the splenic region in the presence of conditions in which embolism is common Infarction may be caused also by thrombosis in situ

Amyloid Spleen — This is to be suspected in association with chronic suppurative diseases

Tuberculosis — So called primary splenomegaly of tuberculous etiology may be present if there is a history of former tuberculous peritonitis or if shadows suggestive of calcified tubercles are identified roentgenologically Inactive tuberculosis of the spleen occurs as a coincidental finding in other types of splenomegaly

Mycosis Glanders Leprosy and Beri beri — Splenomegaly occurs as a secondary manifestation

Ectopic and Movable Spleen — The contour, edge and notch may be identified and perisplenic friction detected The spleen is absent from its normal situation A mass that apparently is a pelvic tumor may be the spleen

Aneurysm of Splenic Artery — This may be associated with splenomegaly its presence is suspected by detection of a murmur either anteriorly or posteriorly, near the spinal column

TONKOFF W Die Entwickelung der Milz bei den Amnioten Arch f mikr Anat 1900 LVI 39
WEIDENREICH Die Blutlymphdrüsen und ihre Beziehung zu Milz und Lymphdrusen Verhandl d Anat Gesellsch 1902 XVI 47
WILSON L B The pathology of splenomegaly a study of the operative and autopsy material from the Mayo Clinic Surg Gynec and Obst 1913 XVI 240
Pathology of spleens removed for certain abnormal conditions of the blood Ann Surg 1915 LXII 158

Hemolytic Icterus

BALFOUR D C Surgery of the spleen Internat. Abstr Surg., 1918 XXVI 1
CHAUFFARD A Pathogenie de l'ictere congenitale de l'adulte Semaine med 1907 XXVII 25
CHAUFFARD A Les icterus hemolytiques Semaine med 1908 XXVIII 49
CHAUFFARD A Pathogenie de l'ictere hemolytique congenitale Ann d med 1914 I 1
ELLIOTT C A and KANAVEL A B Splenectomy for hemolytic icterus a discussion of the familial and acquired types with a report of splenectomized cases Surg Gynec and Obst 1915 XXI 21
GIFFIN H Z Hemolytic jaundice a review of seventeen cases Surg, Gynec and Obst 1917 XXV 152
GIFFIN H Z Hemoglobinuria in hemolytic icterus Arch Int Med 1923 XXXI 573
GIFFIN H Z and BROWN G E Blood volume preceding and following splenectomy in hemolytic icterus and splenic anemia Jour Clin Investigation 19 9 VII 283
GRAM H C Microcytosis with hemolytic icterus Hospitalstidende 1921 LXIV 294
HAYEM Ictere chronique plenomegalique Semaine med 1908 XXVIII 57
KRUMBHAAR E B Experimental and clinical studies in hemolytic jaundice with special reference to the effect of splenectomy Jour Am Med Assn 1914 LXIII 2 56
MAYO W J Hemolytic jaundice Surg Clin N Amer 1921, I 1316
MINKOWSKI O Ueber hereditare unter dem Bilde eines chronischen Icterus mit Urobilinurie Splenomegalie und Nierensiderosis verlaufend Affection Verhandl. d Cong f inn Med 1900 XVIII 316
VAQUEZ H and GIROUX Ictere chronique acholurique avec splénomégalie ses relations avec l'anemie hemolytique Bull et Mem Soc med d Hop de Par, 1907 XXIV 1184
WIDAL F ABRAMI P and BRULE M Differenciation de plusieurs type d'icteres hemolytiques par la procedé des hematies deplasmatisees Presse med 1907 XV 641

GAMNA CARLO Su le lesioni siderotiche che si riscontrano nelle splenomegalie atoniche Pathologica 1924 XVI 203
GANDY C Lesions particulieres de la rate dans un cas de cirrhose biliaire Bull de la Soc Anat 1905 LXXX 872
GIBSON A G On the infective nature of certain cases of splenomegaly and Banti s disease Quart Jour Med 1914 VII 153
GIBSON A G A new pathogenic form of streptothrix Jour Path and Bacteriol 1920 XXIII 357
GIBSON A G The Mycoses of the Spleen MacMillan and Co New York 1930
KRUMBHAAR E B Functions of the spleen Physiol Rev 19 6 VI 160
KRUMBHAAR E B and MUSSER J H Jr The effect of splenectomy on the hematopoietic system of macacus rhesus Arch Int Med 1923 XXXI 686
KUPFER C Ueber Sternzellen der Leber Arch f mikr Anat 18,6 XII 353
LAGUESSE E Le tissu splenique et son developement Anat Anz 1891 VI 131
MacCARTY W C Chronic splenomegaly Arch Int Med 1928 XLI 536
MALL F P The lobule of the spleen Johns Hopkins Hosp Bull, 1898 IX 218
MALL F P On the circulation through the pulp of the dog s spleen Am Jour Anat 1903 II 315
MANN F C BOLLMAN J L and MAGATH T B Studies on physiology of the liver IX The formation of bile pigment after total removal of the liver Am Jour Physiol 1924 LXIX 393
McNEE J W The spleen its structure functions and diseases Lancet 1931 I 951 1009 1063
NIEMANN ALBERT Ein unbekanntes Krankheitsbild Jahrb f Kinderh LXXIX 1
RANVIER L Des clasmatocytes Arch d Anat micr 1899–1900 III 122
ROUS PEYTON Destruction of the red blood corpuscles in health and disease Physiol Rev 19 3 III 75
ROUS PEYTON and ROBERTSON O H The normal fate of erythrocytes Jour Exper Med 1917 XXV 651
SABIN FLORENCE R The development of the spleen In Vol II Keibel Franz and Mall F P Manual of Human Embryology J B Lippincott Co Philadelphia 1912
SABIN FLORENCE R DOAN C A and CUNNINGHAM R S Discrimination of two types of phagocytic cells in the connective tissues by the supravital technique Carnegie Institution of Washington Washington D C Contributions to embryology No 8 1925 125
SACKS BENJAMIN The reticulo endothelial system Physiol Rev 1926 VI 504
STENGEL ALFRED Varieties of splenic anemia Am Jour Med Sc 1904 CXXVIII 497
THIEL C A and DOWNEY HAL The development of the mammalian spleen with special reference to its hematopoietic activity Am Jour Anat 1921 XXVIII 279

TONKOFF W Die Entwickelung der Milz bei den Amnioten Arch f mikr Anat 1900 LVI 39
WEIDENREICH Die Blutlymphdrüsen und ihre Beziehung zu Milz und Lymphdrusen Verhandl d Anat Gesellsch 1901 XV 47
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CHAUFFARD A Pathogenie de l ictere hemolytique congenitale Ann d med 1914 I 1
ELLIOTT C A and KANAVEL A B Splenectomy for hemolytic icterus a discussion of the familial and acquired types with a report of splenectomized cases Surg Gynec and Obst 1915 XXI 1
GIFFIN H Z Hemolytic jaundice a review of seventeen cases Surg Gynec and Obst 1917 XXV 15
GIFFIN H Z Hemoglobinuria in hemolytic icterus Arch Int Med 1923 XXXI 573
GIFFIN H Z and BROWN G E Blood volume preceding and following splenectomy in hemolytic icterus and splenic anemia Jour Clin Investigation 19 9 VII 283
GRAM H C Microcytosis with hemolytic icterus Hospitalstidende 1921 LXIV 294
HAYEM Ictere chronique splenomegalique Semaine med 1908 XXVIII 57
KRUMBHAAR E B Experimental and clinical studies in hemolytic jaundice with special reference to the effect of splenectomy Jour Am Med Assn 1914 LXIII 2256
MAYO W J Hemolytic jaundice Surg Clin N Amer 1921 I 1316
MINKOWSKI O Ueber hereditare unter dem Bilde eines chronischen Icterus mit Urobilinurie Splenomegalie und Nierensiderosis verlaufend Affection Verhandl d Cong f inn Med 1900 XVIII 316
VAQUEZ H and GIROUX Ictere chronique acholurique avec splenomegalie ses relations avec l anemie hemolytique Bull et Mem Soc med d Hôp de Par 1907 XXIV 1184
WIDAL F ABRAMI P and BRULE M Differenciation de plusieurs type d ictères hemolytiques par la procede des hematies deplasmatisees Presse med 1907 XV 641

Splenic Anemia and the Banti Syndrome

BALFOUR D C Surgery of the spleen Oxford Surgery Pt. 1 Vol III 205 Oxford Univ Press New York 1918
BANTI G Dell anemia splenica Arch d Scuola d Anat patol 1883 II, 53
BANTI G Spleneomegalie mit Lebercirrhose Beitr z path Anat u z allg Path, 1898 XXIV 1
GIFFIN H Z Clinical observations concerning twenty seven cases of splenectomy Am Jour Med Sc 1913 CXLV 781
GIFFIN H Z Present status of splenectomy as a therapeutic measure Minnesota Med 1921 IV 132
CRETSEL Ein Fall von Anæmia splenica bei einem Kinde Berl Klin Wchnschr 1866 III 21
MAYO W J Relation of chronic fibrosis and thrombophlebitis of the spleen to conditions of blood and of the liver Arch Surg 1921 II 185
MAYO W J A review of 500 splenectomies with especial reference to mortality in end results Ann Surg 1928 LXXXVIII 409
OSLER WILLIAM On splenic anæmia Am Jour Med Sc 1900 CXIX 54
PEMBERTON J deJ Report of surgery of thyroid gland and spleen 1930 Proc Staff Meetings of Mayo Clinic 1931 VI 151

Chronic Infectious Splenomegaly and Primary Portal Thrombophlebitis

BARGEN J A and GIFFIN H Z Further observations on chronic ulcerative colitis associated with splenomegaly Med Clin N Amer 1930 XIV 591
BROWN W L Pylephlebitis St Barth Hosp Rep 1901 XXXVII 53
CHEVALLIER P Les syndromes porto radiculaires chroniques La place qu occupe en nosographie les splenomegalies inflammatoires chroniques Bull med 1927 XLI 640
GIFFIN H Z The diagnosis of diseases associated with enlargement of the spleen Journal Lancet 1913 XXXIII 97
MAYO W J The relation of chronic fibrosis of thrombophlebitis of the spleen to conditions of the blood and of liver Arch Surg 1921 II 185
VERTAN F Bericht uber einen durch Milz venenthrombose bedingten Fall von Splenomegalie Zentralbl f Chir 1930 LVII 1342
WARTHIN A S The relation of thrombophlebitis of the portal and splenic veins to splenic anæmia and Banti s disease Internat Clinics 20th s 1910 IV 189
WEBSTER L F Portal thrombosis Bull Johns Hopkins Hosp 1921 XXXII 16

Syphilitic Splenomegaly

FURNO A Syphilis of spleen Policlinico (sez med) 19 XXIX 123 (Abstr Jour Am Med Assn 1922 LXXVIII 1579)
GIFFIN H Z The treatment by splenectomy of splenomegaly with anemia associated with syphilis Am Jour Med Sc 1916 CLII 5

KORNS H M Tertiary syphilis of liver simulating Banti s syndrome with report of a case and review of the literature Am Jour Med Sc 1930 CLXXIX 511
LABBÉ M and DELILLE A Syphilis héréditaire precoce avec splénomégalie anémie et reaction du sang guerie par le traitement Gaz d Mal infant 1903 V 97
LUSNE Chronic splenomegaly in inherited syphilis Medecine 19 0 I 686
OLIVARY F A GREENE C H and ROWNTREE L G Diseases of the liver VIII The various types of syphilis of the liver with reference to tests for hepatic function Arch Int Med 19 9 XLIV 133
SUMMERS DOUGLAS A variety of massive syphilitic splenomegaly attended by remarkable vascular changes Surg Gynec and Obst XXVIII 58
WILE U J Visceral syphilis Arch Dermat and Syph 19 1 III 114

Gaucher s Disease

BLOOM WILLIAM Splenomegaly (type Gaucher) and lipoid histiocytosis (type Niemann) Am Jour Path 1925 I 59
BLOOM WILLIAM and KERN RUTH Spleens from Gaucher s disease and lipoid histiocytosis the chemical analysis Arch Int Med 1927 XXXIX 456
LOVEY M B Splenectomy in Gaucher s disease Arch Surg 1930 XXI 851
BOVAIRD DAVID JR Primary splenomegaly endothelial hyperplasia of the spleen Am Jour Med Sc 1900 CXX 377
BRILL N E Primary splenomegaly with a report of three cases in one family Am Jour Med Sc 1901 CXXI 377
BRILL N E and MANDELBAUM F S Large cell splenomegaly (Gaucher s disease) a clinical and pathologic study Am Jour Med Sc 1913 CXLVI 863
EPSTEIN EMIL and LORENZ KARL Die Phosphatidzellverfettung der Milz bei Niemann Pickscher Krankheit verglichen mit der Lipoidchemie des Morbus Gaucher und der Schuller Christianschen Krankheit Ztschr f physiol Chem 1930 CXCII 145
FISCHER A W Quoted by Hirschfeld Hans and Muhsam R Chirurgie der Milz Ferdinand Enke Stuttgart 1930
GAUCHER P C E De l epithelioma primitif de la rate hypertrophie idiopathique de la rate sans leucemie These de Paris 1882
MANDELBAUM F S and DOWNEY HAL The histo-pathology and biology of Gaucher s disease (large cell splenomegaly) Folia Hæmatol 1916 XX 139
MILCH HENRY AND POMERANZ MAURICE Bone changes in Gaucher s splenomegaly Ann Surg 19 9 LXXXIX 552
OPPENHEIMER B S WELT SARA and ROSENTHAL N Recent observations on the Gaucher type of splenomegaly Tr A sn Am Phys 1928 XLIII 136
WELT SARA ROSENTHAL NATHAN and OPPENHEIMER B S Gaucher s splenomegaly with especial reference to skeletal changes Jour Am Med Assn 1929 XCII 637

Malarial Splenomegaly

CARTOLARI Splenectomy in malaria Gazz d Osp 1919 XL 802
COVELL G and BAILEY J D Observations on malaria in the Andamans with especial reference to the enlarged spleen in adults Indian Jour Med Res 1927 XV 309
JIMÉNEZ R and FITTALUGA G Recurring malaria after splenectomy Arch de Cardiol y Hematol 1921 II 233 Abstr Jour Am Med Assn 1921 LXXVII 896
MOURDAS The complications and the surgical treatment of the malarial spleen Internat Clin 1910 I 158
OLGIATI Des indications de la splenectomie dans l'hypertrophie malarique de la rate These de Paris 1896

Tropical Splenomegaly

CASTELLANI ALDO and CHALMERS A J Manual of Tropical Medicine Ed 3 Bailliere Tindall and Cox London 1919
COLEMAN F B and BATEMAN J L Splenectomy in Egyptian splenomegaly Lancet 1924 II 1176
DARLING S T Histoplasmosis a fatal infectious disease resembling kala azar found among the natives of tropical America Arch Int Med 1908 II 107
MANSON PATRICK Manson s Tropical Diseases a Manual of the Diseases of Warm Climates Ed 8 W Wood and Co London 1925
RICHARDS OWEN Splenectomy in Egyptian splenomegaly Brit Jour Surg, 1914 I 419
STITT E R The Diagnostics and Treatment of Tropical Diseases Ed 5, P Blakiston s Son and Co Philadelphia 1929
STRONG R P Medical report of the Hamilton Rice Seventh expedition to the Amazon Contribution from the Harvard Inst for Trop Biol and Med No 4 1926

Splenomegaly with Anemia in Infancy (including von Jaksch s Disease)

ASHBY H T The anemia associated with rickets and gastro intestinal disturbances including splenic anemia in children Practitioner 1912 LXXXVIII 675
CHIARI H Ein Beitrag zur Kenntnis der sogenannten foetalen Erythroblastosis Jahrb f Kinderh 1914 LXXX 501
COOLEY T B Von Jaksch s anemia Am Jour Dis Child 1927 XXXIII 786
COOLEY T B Likenesses and contrasts in the hemolytic anemias of childhood Am Jour Dis Child 1928 XXXVI 1 57
COOLEY T B WITWER E R and LEE PEARL Anemia in children with splenomegaly and peculiar changes in the bones report of cases Am Jour Dis Child 1927 XXXIV 347

EVANS F A and HAPP W M Secondary anemia of infants Bull Johns Hopkins Hosp 19 XXXIII 1
GIFFIN H Z Splenectomy for splenic anemia in childhood and for the splenic anemia in infancy Ann Surg 1915 LXII 679
von JAKSCH R Ueber Leukamie und Leukocytose im Kindesalter Wien klin Wchnschr 1889 II 435
von JAKSCH R Ueber Leukamie und Leukocytaemia Infantum Pseudoleucaemia Wien med Wchnschr 1889 XXXIX 854
KENNEDY R I J Disease of children benefited by splenectomy Jour Am Med Assn 1928 XCI 874
STILLMAN R G A study of von Jaksch s disease Am Jour Med Sc 1917 CLIII 218
WHITCHER B R Erythroblastemia of infants (von Jaksch s disease) Am Jour Med Sc 1930 CLXXIX 36

Hemorrhagic Purpura

BRILL N E and ROSENTHAL N The curative treatment by splenectomy of chronic thrombocytopenic purpura hemorrhagica Am Jour Med Sc 1923 CLXVI 503
BRILL N E and ROSENTHAL N Treatment by splenectomy of essential thrombocytopenia (purpura hemorrhagica) Arch Int Med 1923 XXXII 939
CONNER H M and BUMPUS H C JR Essential hematuria and its possible relationship to purpura hemorrhagica Am Jour Med Sc 1927 CLXXIII 1,6
DUKE W W The relation of blood platelets to hemorrhagic disease description of a method for determining the bleeding time and coagulation time and report of three cases of hemorrhagic di ease relieved by transfusions Jour Am Med Assn 1910 LV 1185
EVANS W H Blood changes after splenectomy in splenic anemia purpura hemorrhagica with special reference to platelets and coagulation Jour Path and Bacteriol 1928 XXXI 815
FRANK E Die essentielle Thrombopenie (Konstitutionelle Purpura Psuedo-Hamophilie) Berl klin Wchnschr 1915 LII 454
GIFFIN H Z Unusual types of hemorrhagic disease Am Jour Med Sc 1928 CLXXV 44
GIFFIN H Z and HOLLOWAY J K Hemorrhagic purpura Med Clin N Amer 1923 VII 241
GIFFIN H Z and HOLLOWAY J K A review of twenty eight cases of purpura hemorrhagica in which splenectomy was performed Am Jour Med Sc 1925 CLXX 186
KAZNELSON PAUL Verschwinden der hamorrhagischen Diathese bei einem Falle von essentieller Thrombopenie (Frank) nach Milzexstirpation Splenogene thrombolytische Purpura Wien klin Wchnschr 1916 XXIX 1451
KAZNELSON PAUL Thrombolyti che Purpura Ztschr f klin Med 1919 LXXXVII 133

MARSH H D Splenectomy in acute hemorrhagic purpura Tr Assn Res and Ex Res Physicians Mayo Clinic 19 9 X 147
MINOT G R Studies on a case of idiopathic purpura hemorrhagica Am Jour Med Sc 1916 CLII 48
OSLER WILLIAM On a family form of recurring epistaxis associated with multiple telangiectases of the skin and mucous membranes Bull Johns Hopkins Hosp 1901 XII 336
O LEARY P A and CONNER H M Acute purpura hemorrhagica as complication in the treatment of syphilis Am Jour Physiol 1925 IX 6
SWEENEY J S Chronic aplastic anemia and symptomatic hemorrhagic purpura probably due to benzol poisoning Am Jour Med Sc 19 8 CLXXV 317
WHIPPLE A O Splenectomy as a therapeutic measure in thrombocytopenic purpura hemorrhagica Surg Gynec and Obst 19 6 XLII 3 9

Leukemia

DAMESHEK WILLIAM Acute monocytic (histiocytic) leukemia Arch Int Med 1930 XLVI 718
GIFFIN H Z Splenectomy Surg Gynec and Obst 19 7 XLV 577

Eosinophilic Hyperleukocytosis with Splenomegaly

ARMAND-DELILLE P and PIERREDON Hyperluecocytose avec eosinophilie tres elevee (76 p 100) et splenomegalie Bull Soc de Pediat de Par 19 7 XXV 424
GIFFIN H Z Persistent eosinophilia with hyperleukocytosis and splenomegaly Am Jour Med Sc 1919 CLVIII 618
HARRISON F F Eosinophilia with splenomegaly Am Jour Med Sc 1930 CLXXIX 208
STILLMAN R G A case of myeloid leukemia with predominance of eosinophilic cells Med Rec 1912 LXXXI 594

Polycythemia Vera

BLAD AXEL Et Tilfaelde af Polyglobulie med Miltsvulst Folia Haematol 1905 II 685
COMINOTTI V Hyperglobulie und Splenomegalie Wien klin Wchnschr 1900 XIII 881
GIFFIN H Z The treatment of polycythemia vera (erythremia), In Blumer George the Billings Forcheimer Therapeusis of Internal Disease Vol IV 461 D Appleton and Co New York 19 9
GIFFIN H Z and BROWN G E Studies of capillaries and blood volume in polycythemia vera Am Jour Med Sc 19 3 CLXVI 489

GIFFIN H Z and CONNER H M The untoward effects of treatment by phenyl hydrazine hydrochloride Jour Am Med Assn 19 9 XCII 1505
SCHNEIDER N Ein Beitrag zur Frage der Polyglobulie Wien Klin Wchnschr 1907 XX 413

Sickle cell Anemia

COOLEY THOMAS and PEARL LEE The sickle cell phenomenon Am Jour Dis Child 1926 XXXII 334
LANDON J F and LYMAN A V Sickle cell anemia with case report of splenectomy Am Jour Med Sc 1929 CLXXVIII 223
SYNDENSTRICKER V P Further observations on sickle cell anemia Jour Am Med Assn 1924 LXXXIII 12

Agranulocytic Anemia

BALDRIDGE C W and NEEDLES R J Idiopathic neutropenia Am Jour Med Sc 1931 CLXXXI 533
BLUMER GEORGE The agranulocytic blood picture in conditions other than angina Am Jour Med Sc 1930 CLXXIX 11
BROWN P K A fatal case of acute primary infectious pharyngitis with extreme leukopenia Am Med 190 III 649
CONNER H M MARGOLIS H M BIRKELAND I W and SHARP J F Agranulocytosis and hypogranulocytosis Arch Int Med (In press)
FARLEY D L Depressed bone marrow function from the arsphenamins (including a type of so called agranulocytosis) Am Jour Med Sc 1930 CLXXIX 214
FRIEDEMANN ULRICH Über Angina agranulocytotica Med Klin 19 3 II 1357
HARKINS H N Granulocytopenia and agranulocytic angina with recovery Arch Int Med 1931 XLVII 408
HUEPER W C Agranulocytic angina (Schultz) and the agranulocytic symptom complex Arch Int Med 1928 XLII 893
KASTLIN G J Agranulocytic angina Am Jour Med Sc 1927 CLXXIII 700
LOVETT BEATRICE P Agranulocytic angina Jour Am Med Assn 1924 LXXXIII 1498
ROBERTS S P and KRACKE R R Agranulocytosis Jour Am Med Assn 1930 XCV 780
SCHULTZ WERNER Ueber eigenartige Halserkrankungen Deutsch med. Wchnschr 19 2 II 1495
TAUSSIG A E Personal communication to the author

Abscess of the Spleen

ELTING A W Abscess of the spleen Ann Surg 1915 LXII 182
Vol. IV 1231

MARSH H D Splenectomy in acute hemorrhagic purpura Tr Assn Res and ex Res Physicians Mayo Clinic 19 9 X 147

MINOT G R Studies on a case of idiopathic purpura hemorrhagica Am Jour Med Sc 1916 CLII 48

OSLER WILLIAM On a family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes Bull Johns Hopkins Hosp, 1901 XII 338

O LEARY P A and CONNER H M Acute purpura hemorrhagica as complication in the treatment of syphilis Am Jour Physiol 19 5 IX 6

SWEENEY J S Chronic aplastic anemia and symptomatic hemorrhagic purpura probably due to benzol poisoning Am Jour Med Sc 19 8 CLXXI 31

WHIPPLE A O Splenectomy as a therapeutic measure in thrombocytopenic purpura hemorrhagica Surg Gynec and Obst 19 6 XIII 3 0

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COMINOTTI V Hyperglobulie und Splenomegalie Wien klin Wchnschr 1900 XIII 881

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BLUMER GEORGE The agranulocytic blood picture in conditions other than angina Am Jour Med Sc 1930 CLXXIX 11
BLOWN I K A fatal case of acute primary infectious pharyngitis with extreme leukopenia Am Med 190 III 649
CONNER H M MARGOLIS H M BIRKELAND I W and SHARP J E Agranulocytosis and hypogranulocytosis Arch Int Med (In press)
FARLEY D L Depressed bone marrow function from the arsphenamin (including a type of so-called agranulocytosis) Am Jour Med Sc 1930 CLXXIX 214
FRIEDEMANN ULRICH Über Angina agranulocytotica Med Klin 1923 II 1357
HARKINS H N Granulocytopenia and agranulocytic angina with recovery Arch Int Med 1931 XLVII 408
HUEPER W C Agranulocytic angina (Schultz) and the agranulocytic symptom complex Arch Int Med 19 8 XLII 893
KASTLIN C J Agranulocytic angina Am Jour Med Sc 1927 CLXXIII 799
LOVITT BEATRICE R Agranulocytic angina Jour Am Med Assn 1924 LXXXIII 1498
ROBERTS S R and KRACKE R R Agranulocytosis Jour Am Med Assn 1930 XCV 780
SCHULTZ WERNER Ueber eigenartige Halserkrankungen Deutsch med Wchnschr 19 II 1495
TAUSSIG A I Personal communication to the author

Abscess of the Spleen

ELTING A W Abscess of the spleen Ann Surg 1915 LXII 182

Ectopic and Movable Spleen

CATSARAS J Volstandige Nekrose einer Wandermilz mit kompensatorischer p pherischer vielknotiger Hyperplasie von Milzgewebe Virchow s Arch f p Anat u Physiol 1928 CCLXVIII 181
HALL J B Splenopexy for wandering spleen with report of a case Ann Surg 1903 XXXVII 481
LAHEY F H Prolapsed spleen with acute torsion splenopexy with table of un reported cases to date Ann Surg 1911 LIV, 612
RUMMEL HANS Stieldrehung einer Wandermilz unter dem klinischen Bild der Stieldrehung eines Ovarialtumors verlaufend Munchen med Wchnschr, 19 9 LXXVI 371
SALIBA JOHN Dislocation of the spleen Surg Gynec and Obst 1918 XXVII 75
SALVIN A A Ectopic spleen causing intestinal obstruction Ann Surg 1930 XCII 63
SEN J N An enlarged wandering spleen mistaken for an ovarian tumour splenec tomy and recovery Indian Med Gaz 1925 LX 576
SUTTON J E JR Wandering spleen with torsion of its pedicle Ann Surg 1925 LXXXII 39

Aneurysm of the Splenic Artery

GOODHART J F Arterio venous aneurysm of splenic vessels with thrombosis of mesenteric veins and localized acute colitis Tr Path Soc London 1889 XL 67
POOL E H and STILLMAN R G Surgery of the Spleen, D Appleton and Co New York 1923

Cysts and Tumors

BOYD DOUGLAS Echinococcus cyst of the spleen Boston Med and Surg Jour 19 5 CXCIII 591
CUMSTON C C The evolution of hæmatic cysts of the spleen Internat Clin s 13 1920 II 12
DOWD C N Cavernous angioma of the spleen Ann Surg 1915 LXII 177
FOWLER R H Pathological aspects of primary tumors of the spleen Long I land Med Jour 1911 V 65
FOWLER R H Cysts of the spleen Ann Surg 1913 LVII 658 Surgery of cysts of the spleen Ann Surg 19 1 LXXIV 20
GOLDSTEIN H J Primary sarcoma of the spleen Reports of cases of plenic sarcoma Review of the literature Am Jour Surg 19 XXXVI 57
GORDON E Ein Fall von Splenektomie wegen Milzechinokokkus Klin Med 1926 IV 389

JOHNSTON G B Non parasitic cysts of the spleen Surg Gynec. and Obst 1908 VI 615
KUMARIS J Milzdermoid und Wandermilz Arch f klin Chir 1915 CVI 699
MILLS H W Hydatid cyst of the spleen with report of four cases Surg Gynec and Obst 19 4 XXXVIII 491

Rupture

BERGER ERICH Die Verletzungen der Milz und ihre chirurgische Behandlung Arch f klin Chir 1902 LXVIII 768
CONNORS J F Splenectomy for trauma Ann Surg 19 8 LXXXVIII 388
DRETZKA LEO Rupture of the spleen report of twenty seven cases Surg Gynec and Obst 1930 LI 258
HARRIS N G A case of rupture of the spleen after artificial induction of malaria Lancet 1928 II 500
LEIGHTON W L Spontaneous rupture of malarial spleen with abstract of cases reported between 1842 and 19 1 Ann Surg 1921 LXXIV 13
McINDOE A H Delayed hemorrhage following traumatic rupture of spleen Proc Staff Meetings of Mayo Clinic 1928 III 365
TOOL E H Injuries to the spleen Boston Med and Surg Jour 1923 CLXXXVIII 262
TWITCHELL E W Spontaneous rupture of spleen following malarial therapy for general paresis report of a case California and West Med 1930 XXXIII 512

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Ectopic and Movable Spleen

CATSARAS J Volstandige Nekrose einer Wandermilz mit kompensatorischer p pherischer vielknotiger Hyperplasie von Milzgewebe Virchows Arch f p Anat u Physiol 19 8 CCLXVIII 181
HALL J B Splenopexy for wandering spleen, with report of a case Ann Surg 1903 XXXVII 481
LAHEY F H Prolapsed spleen with acute torsion splenopexy, with table of un reported cases to date Ann Surg 1911 LIV 61
RUMMLL HANS Stieldrehung einer Wandermilz unter dem klinischen Bild der Stieldrehung eines Ovarialtumors verlaufend, Munchen med Wchnschr 1929 LXXVI 371
SALIBA JOHN Dislocation of the spleen Surg, Gynec and Obst 1918 XXVII 73
SALVIN A A Ectopic spleen causing intestinal obstruction Ann Surg 1930 XCII 63
SEN J N An enlarged wandering spleen mistaken for an ovarian tumour splenec tomy and recovery Indian Med Gaz 1925 LX 576
SUTTON J E Jr Wandering spleen with torsion of its pedicle Ann Surg 19 5 LXXXII 39

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DOWD C N Cavernous angioma of the spleen Ann Surg 1915 LXII 177
FOWLER R H Pathological aspects of primary tumors of the spleen Long Island Med Jour 1911 V 265
FOWLER R H Cysts of the spleen Ann Surg 1913 LVII 658 Surgery of cysts of the spleen Ann Surg 1921 LXXIV 20
GOLDSTEIN H J Primary sarcoma of the spleen Reports of cases of splenic sarcoma Review of the literature Am Jour Surg 1922 XXXVI 57
GORDON E Ein Fall von Splenektomie wegen Milzechinokokkus Klin Med 1926 IV 389

CHAPTER IV

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Introduction

Gout gicht (German) gôta (Spanish), goutte (French) and gotta (Italian) respectively have been adapted from the Latin etymon gutta which implies a drop or coagulation It is descriptive of the articular dyscrasia thought to be caused by a defluxion of humors into affected joints The term is applicable microscopically as well as macroscopically The chalky tophus which is accepted as the hallmark of clinical gout is essentially a large accumulation of sodium urate crystals However a large deposit must have a beginning and a microscopic gutta of urate is probably the initial lesion in all affected structures Until such a time as the etiology of the malady is understood and the pathogenesis is clarified there should be no objection by the nosographer to the retention of the term gout

This discussion of gout was compiled with a twofold purpose Firstly it aims to portray an accurate description of clinical gout This is appropriate since the failure of detection of the various manifestations has delayed recognition of the potential incidence of the malady Secondly a considerable effort has been expended by the writer during the past decade in researches which pertain to the metabolic phenomena of the gouty dyscrasia Clinical and investigative studies have been pursued concomitantly at the Massachusetts General Hospital The results of this published in part only are brought together here for the first time

History

Gout is a malady fairly entitled to boast of its great antiquity as it was probably one of the earliest diseases to which flesh became heir when man began to participate in the luxuries of civilized life it is a disease also which can lay claim to having had among its victims some of the most renowned of the human race from their position opulence and intellect Thus wrote Garrod[5] nearly seventy five years ago Sydenham[117] noted a century prior to this observation that great kings emperors generals admirals and philosophers have died of gout The prevalence of gout among all classes of modern society lends credence to the statement expressed by contemporary masters that the incidence and distribution of gout throughout the civilized world changes but little through the centuries

Hippocrates[71] 460–370 B C is accredited with the first description in recorded history of podagra the appellation used in ancient and medieval times It seems reasonable to believe however that Hieron

Fifth Century B C of Syracuse[7] recognized the malady prior to Hippocrates since he commented on the association of bladder stones and joint disease possibly urate calculi in patients with gouty arthritis. Other physicians in ancient times who presumably were well acquainted with the malady include Galen[74] Seneca[49] Aretaeus of Cappadocia (Second Century[2]) and Caelius Aurelianus (Fifth Century). Aretaeus noted that the great toe is attacked first that sometimes the disease is confined to the feet at other times it involves the hands elbows knees and hips and that occasionally tophi appear. The overwhelmingly male preponderance was mentioned also by him. Alexander of Tralles[49] made a significant advance in the treatment of gouty arthritis in the sixth century A D by the successful use of hermodactyl colchicum autumnale the herb from which colchicine is derived. Gilbert[63] recognized the Alexandrian discovery in the thirteenth century and referred to the colchicine preparation which he used in his practice as Cathopcie Alexanderine. In 18 0 Pelletier and Caventou[170] isolated the alkaloid colchicine from the meadow saffron or colchicum autumnale.

The association of uric acid and gout is almost as old as our nation. Indeed it was in 1776 that Scheele[133] identified uric acid as a constituent of urine. A more pertinent observation was made in 1787 by Wollaston[illegible] who isolated uric acid from gouty tophi. This was confirmed a few years later by Pearson[11]. It is noteworthy that in 1793 Forbes[52] speculated on the possibility of an increased concentration of lithic acid as uric acid was called at that time[159] in the *blood* of patients with gout. Clinical methods were not available to test this hypothesis and it was not until after a lapse of half a century that Garrod[6] demonstrated an increased content of uric acid in the serum of afflicted persons. This was accomplished by an ingenious technique which he described as the uric acid thread experiment. Two or three ounces of blood were drawn by cupping or by venepuncture from a patient suspected of having gout. A cotton thread was placed in the drawn whole blood and allowed to remain for several days. The urate crystals gradually precipitated out and around the imbedded thread. The content of urate was relatively low in non gouty bloods and few or no crystals were attracted to the thread. The thread method was sufficiently quantitative that Garrod was able to make an approximate estimate of urate values in serum. The data from five gouty patients as determined by the thread test varied between 2 5 and 17 mgm per 100 c c. The mean is not dissimilar from concentrations measured by modern analytical methods. The classification of uric acid as a purine body by Emil Fischer[39,40] is the last milestone to date in the history of gout.

Definition

Gout was known to the ancients as podagra a Greek derivation from *pous* foot and *agra* attack (Fig 1) The selection is not surprising since gouty arthritis appears first in the feet in the majority of afflicted persons The term is a limited one however and if the Greek roots



Fig 1 Gouty feet laden with subcutaneous and osseous tophi patient No 74 Circumference of right ankle almost twice as great as before appearance of urate deposits fifth toe on right site of discharging tophus x ray of right foot taken in same year shown in Figs 38 and 39

were retained we should call gouty hands (Fig 2) *chiragra* gouty knees *dentagra* and gouty hips *sciatica* The advantages of the inclusive Latin stem are apparent Radulfe is accredited[5] with the introduction of the Latin derivation during the thirteenth century There is an earlier reference, however in an old English manuscript of the tenth century which suggests a prior use There cam a goute In is knee of Anguische gret so longue that is kneo to swal

Many adjectives have been employed to qualify the term gout or have been used to describe the clinical syndrome and its capricious variations These include acute gouty arthritis interval gout chronic deforming gouty arthritis regular gout irregular gout retrocedent gout metastatic gout acute recurrent gouty arthritis atypical gout visceral gout allergy gout lead gout renal gout and gouty diathesis[119] The number is unnecessarily large and many of the terms are repetitious This serves to confuse rather than clarify the bona fide clinical picture The gouty nomenclature will be confined to four appellations in this



Fig Gouty hands showing multiple tophi about joints of phalanges patient No 74 For x ray of right hand taken in same year see Fig 35

chapter (1) Gout is the parent term with three clinical subdivisions (2) acute gouty arthritis which may be described more precisely as acute attacks of gouty arthritis (3) intercritical gout and (4) chronic deforming gouty arthritis Acute gouty arthritis and chronic deforming gouty arthritis are orthodox clinical realities They are recognized as such by most observers Intercritical gout covers the period between acute attacks

It will be apparent that gout and gouty arthritis are not identical clinical processes *Gouty arthritis* is the clinical disturbance which produces articular symptoms in a person afflicted with gout It may be acute or chronic *Acute attacks of gouty arthritis* usually are responsible for the patient seeking medical advice and may be superimposed upon chronically deformed gouty joints or upon joints without any demonstrable anatomical changes Acute attacks of gouty arthritis are present only a small portion of the time at any stage of the natural course of the disease *Intercritical gout* is asymptomatic up to the period of appearance of persistent crippling articular processes Low grade symptoms from induced malformations are tenacious once they have appeared *Chronic deforming gouty arthritis* is a late manifestation Several decades usually elapse after the first attack of arthritis before this stage is reached Many patients escape this stage Those who have their first attack after the age of 50 may live the allotted three score and ten without having to suffer from chronic deforming gout

The parent term *gout* or *gout sine joint symptoms* remains to be defined Patients with any of the three above mentioned manifestations of course have gout as well It is known that the concentration of serum uric acid is elevated in gouty persons during the first attack of gouty arthritis A few patients have by chance been studied before the first articular attack and an elevated urate level has been observed in these also[1] The latent tendency may have been present for some extended period of time If gout is a familial dyscrasia it is not unreasonable to assume that persons are born with a proclivity to the malady to wit an increased concentration of serum urate The chemical disturbance may be the only evidence of gout during the intercritical periods in the earlier years of the disease We should prefer to assume that the metabolic dysfunction is gout and consolidate the two expressions into one term *metabolic gout* This would add one more term to the long list of gouty nomenclature and probably would contribute little When the terms acute or chronic gouty arthritis are employed in this chapter the term refers to manifestations that are clinically obvious Gout on the other hand is the underlying metabolic dyscrasia which may not be apparent clinically except upon determination of the concentration of urate in body fluids

The connotation *gouty diathesis* is mentioned frequently in the literature but it has not been adequately defined Duckworth[29] affirmed that the gouty diathesis which is still with us has served our literary convenience rather than the interests of pathology It reminds us of those capacious brackets used by mathematicians for the safe handling

of unknown quantities except that the mathematical formula work toward a solution, whilst diathesis can only perpetuate the problem. Sclerosis of the coronary vessels and gastrointestinal disturbances have been attributed to a gouty diathesis in patients who neither have suffered from acute gouty arthritis nor have been shown to have an increased concentration of urate in the blood. We believe that the use of the term in this association is not justified. *Irregular gout*, *retrocedent gout* and *visceral gout* also are objectionable, since they are vague and have not been used to describe processes caused by urate deposits. If a patient has had one or more attacks of acute gouty arthritis, the unqualified diagnosis of gout is applicable and hedging adjectives are superfluous.

The adjective *gouty* recurs frequently in this chapter since it serves a useful purpose. By gouty we imply an intimate relationship to urate gout and will never use it as an impure term to mean gout-like or simulating gout in order to qualify an otherwise definitive statement.

Heredity

Gout is a familial malady. This fact was recognized by at least two of the ancients, Galen and Caelius Aurelianus. Affirmations that the familial incidence of gout is low[70,108] are refuted by several large series of gouty patients whose family histories show a predominant weakness for the metabolic dyscrasia.[57,77,100,139,163] Some of the discrepancies may be explained by assuming a lack of care in obtaining an extensive family history.[73] A positive family history may be denied if hereditary data are pursued in a careless clinical manner. The hereditary trait may be evident, on the other hand, if the family tree is perused as skillfully by the physician as by the genealogist. The exact mode of transmission of the metabolic dyscrasia has not been deciphered because of the difficulty of any one observer examining a sufficient number of patients and families and collecting sufficient data in order that the observations might be treated as genetic statistics. The most complete series of cases that has been reported was assembled by Scudamore.[139] He observed that the father was afflicted in 87 per cent of the patients who admitted a family history of gout. Futcher[46] expressed the statement which is currently accepted, that if a woman be afflicted she is prone to transmit the malady to her offspring.

The hereditary constitution of gout has received especial attention in the writer's laboratory. In the pursuit of this interest a sociological medical study was made of a group of families in which one or more

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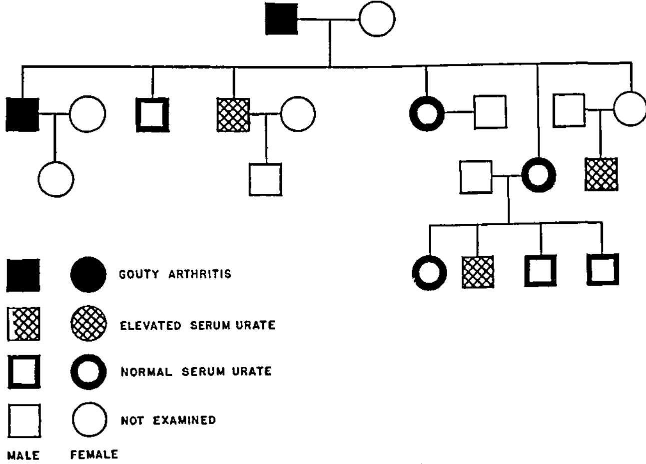


Fig 3 Genealogical tree of gouty patient No 68

members were proven to have gout[151] A total of 136 blood relatives of 27 gouty patients were consulted[15] Attention during the study of the relatives was concentrated upon the following particulars (1) a past history of joint distress (2) physical examination of the joints for the appearance of chronic deforming gouty changes and (3) laboratory studies pertinent to gouty individuals The genealogical data from one family are given in Fig 3 Slightly more than one half of the relatives investigated were males The ages of the subjects varied from 6 to 86 most of them were either in the third fourth or fifth decade of life X rays of the feet were taken of 110 Roentgenological changes consistent with gout were not observed in any It was concluded from the history the physical examination and the x ray examination that no one of the relatives was suffering from gouty arthritis

The negative conclusions could not be carried beyond this point however particularly after the serum uric acid data were available The serum observations were significant and caused us to alter our conception of the incidence of potential gouty arthritis in the group of relatives The concentration of serum uric acid was determined one or more times in each non arthritic relative and was within the range for normals in 102 The remaining 34 subjects 25 per cent however had a serum uric acid greater than 6 0 mgm per 100 c c The values ranged from 6 1 to 10 8 mgm per 100 c c the average was 7 3 mgm The determination was repeated in 13 subjects one or more times and the elevated values were confirmed Concentrations of uric acid above 6 0 mgm are abnormal and are observed typically in patients with one of the three subtypes of clinical gout Eighty per cent of the relatives with an elevated serum urate were males an incidence which agrees with the sex distribution of gouty arthritis The ages ranged from 14 to 86 The serum nonprotein nitrogen was less than 35 mgm per 100 c c in each patient Other tests for kidney function were done in several of the older subjects and all such tests were normal It was concluded from the clinical and laboratory data that causes of an increased uric acid from other conditions than gout might be excluded

The increased concentration of serum urate in non afflicted relatives of gouty patients[41] may be associated intimately with the true gouty constitution Since the first attack of gouty arthritis may appear in any decade of life a life long follow up will be needed to determine the percentage of relatives with hyperuricemia who will eventually develop articular manifestations It seems reasonable to us to assume that the hyperuricemia develops during gestation or shortly after birth The

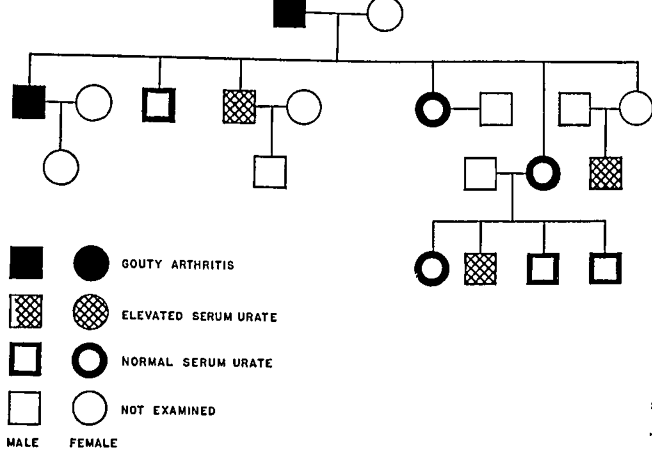


Fig. 3. Genealogical tree of gouty patient No. 68

fact that 3 subjects were older than 70 indicates that an elevated concentration of urate is compatible with good health and a reasonably long life. These data lend support to the hypothesis that an increased formation of uric acid by the body is an etiological component of gout. If this contention be correct, cases of gouty arthritis will develop in gouty families primarily because of the hereditary predisposition[144] while social factors, environmental influences and dietary indiscretions are relegated to a position of secondary importance.

Incidence

Gout is not a rare malady, although the recognition of it may be infrequent. Neither is there believed to be any significant reduction in incidence from generation to generation. Familial maladies tend to maintain a relatively constant incidence and do not become rarer within the life time of any one observer. Hench[68] has affirmed that patients with gouty arthritis constitute at least 5 per cent of all patients seen at the Mayo Clinic suffering from the several diseases of the joints. A similar percentage has been observed in other clinics[55, 86]. If this value is valid throughout the United States, there may be at least a third of a million people suffering from gout among 7 million sufferers from chronic rheumatism[114]. It is safe to estimate that only a portion of this number is diagnosed as gout and treated for same. One reason for the discrepancy between probable incidence and clinical recognition is the common failure among physicians of waiting until advanced tophaceous changes in the joints have appeared before suspecting gouty arthritis. Another reason is the lack of unanimity regarding criteria for a diagnosis. Physicians who are particularly interested in gout, a group which constitutes a very small minority, are apt to have a high percentage of correct diagnoses. Physicians who have only a casual interest in gout may have a significant percentage of incorrect diagnoses, particularly in the earlier years after onset of acute joint symptoms. Whatever may be the correct incidence, sufficient data are already available to disprove the contention that gout is a rare malady.

Sex. — Gout manifests an overwhelming affinity for the male. The published data on sex distribution show that less than 5 per cent of those afflicted are females. Particular caution should be exercised in confirming a suspected diagnosis in a member of this sex, so infrequently are they affected. The development of urate tophi is conclusive proof, of course. In the earlier stages of the disease all of the diagnostic criteria should be applied rigidly before a commitment is made.

Hippocrates maintained that females are stricken with acute gouty arthritis only after the menopause. Among the females in our series gouty attacks have increased in frequency and severity after a natural or artificial menopause, but in at least 2 patients attacks have appeared while the patient was menstruating regularly. The aberrant sex ratio may well be attributed to the hereditary transmission of the malady, since there are no other etiological implications in the infrequent occurrence in females. It is possible that gout is transmitted as a sex linked character and the development of the disease in females is a biological anomaly. The presence of gout in a male hermaphrodite[1,2] is an even rarer anomaly.

Race — Gout is widely distributed throughout the world and shows no particular preference for the white man. Several authentic cases in pure blooded native Chinese have been observed by Dieuaide[3] as well as by others[31,56]. An exceptionally high incidence among natives of India has been reported.[4] Few cases have been reported in pure strains of negroes.[10,16] Cohen[1] has published a report of two cases of proven gout in negro brothers, one aged 27, the other 16. The genealogical tree for four generations of the family studied by him is included.

Nationality — Gout recognizes no political boundaries. Americans, Italians, Jews, Germans and Englishmen comprise the majority of patients of our series. There are included also Scandinavians, Russians, Frenchmen and Irishmen.

Age — The first attack of gouty arthritis may appear in childhood[7] or adolescence, or it may develop as late in life as the tenth decade[5]. The earliest attack of acute arthritis appeared at the age of 6 in the group of patients seen at the Massachusetts General Hospital. There have been several patients who had acute symptoms in their teens. The majority, however, did not have an initial attack until the fourth or fifth decade. At the other extreme is one patient who had his first gouty attack at the age of 7. Patients who have joint symptoms early in life tend to develop severe deforming gouty arthritis or serious kidney disease. Crippling deformities of the joints are unusual in patients who develop the first symptoms of joint distress late in life, and clinical evidence of renal or vascular disease is no more advanced than frequently is observed in patients of the same age group who do not have gouty arthritis.

Social Status — There is meagre support for the presumption that gout is a disease of persons who are habitually intemperate whether it be in regard to alcohol, to sexual activity or to food — the sequence

of high living and thorn in the rose of gastronomy, with many years of savoury dinners and fragrant vintages — [34] Many of the gouty patients in our series have been admitted in an impoverished or indigent state to the out patient department and rarely did we obtain in these a history of repeated over indulgence in rich foods and alcoholic beverages Furthermore several of the patients have been supported by charitable organizations almost continuously since the depression days of 1930 with only a subsistence allowance for the necessities of life The incidence of gout and the development of tophaceous deposits among patients in the lower social brackets are quite as high as among those who are more richly endowed The statement of Crafe[56] that typical acute attacks of gout disappeared in Central Europe during World War I does not invalidate the deduction Destitution is associated with biological exigencies that need not be encountered in temperate living

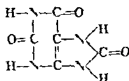
Metabolic Phenomena

Nosographers include gout in most comprehensive presentations of metabolic disorders Such an allocation usually is acceptable although some physicians believe that the designation metabolic disorder has been overworked and should be limited to diseases which are characterized by a disturbance of intermediary metabolism The classification of gout as a metabolic disorder is believed by us to be expedient but our reasons for this are based upon diverse data and not because a disturbance of the intermediary metabolism of nucleoprotein and purine substances has been demonstrated The observations in support of this classification are heterogeneous and cross several categories of physiological and pathological experiences A discussion of the intermediary metabolism of certain nitrogenous substances in man and animals will be given first Emphasis will be placed upon the precursors and the degradation products of uric acid The physical properties responsible for the solubility of it in serum urine and other body fluids then will be discussed and will be followed by a description of the dynamic forces responsible for the excretion of uric acid from the body An account of the disturbance of acid base equilibrium which constitutes the gout cycle will conclude the consideration of metabolic dysfunctions

The term urate is used interchangeably with uric acid throughout most of the review The first term is preferable and it would be better if it were used exclusively in all physiological considerations of uric acid Free acids do not exist as such in high concentrations in the

body. Most biological media are well buffered and are physiologically neutral in reaction. Acids and bases whether strong or weak are present principally as dissociated salts. Thus chloride is present as the dissociated salt of sodium chloride and does not exist as hydrochloric acid. When reference is made to its concentration in the body it is to the chloride ion and not to hydrochloric acid. Similarly phosphate is the usual physiological designation rather than phosphoric acid. Approximately 97 per cent of uric acid exists as the dissociated *monosodium* salt of urate in serum and other body fluids[13] hence the suitability of speaking of urate in lieu of uric acid.

The chemical formula of uric acid was shown by Fischer[40] to be 2-6-8 trioxypurine with the lactam formula



Purine Metabolism

Uric acid is the end product of purine metabolism in humans just as urea is the end product of nitrogenous substances of amino acid and pyrimidin origin. In birds and reptiles uric acid is the end product of most nitrogenous substances whether of purine or of amino acid origin. Most mammals on the other hand excrete significant quantities of urea and only trace of uric acid. The explanation of their ability to do so is related to the presence of the enzyme uricase[145] which oxidizes urate to allantoin. Man and the ape are unique in the precise steps of purine metabolism and occupy an intermediary position between reptiles and certain mammals in so far as the metabolism of nitrogenous products is concerned. The amino nitrogen and pyrimidin nitrogen waste is excreted as urea while the purine nitrogen is excreted as urate because no enzyme is present to oxidize urate to allantoin[38, 145]. If man were endowed with a mechanism which enabled him to oxidize urate gout would not be possible or else it would manifest itself as a different clinical and chemical disturbance.

The uric acid excreted in the urine of man is partially endogenous and partially exogenous. *Approximately 300 milligrams of endogenous* urate are excreted daily[illegible] on a purine free diet with an adequate caloric intake. *The nucleo proteins of the body are the principal source.* The path of breakdown is essentially the same as that of ingested purine

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serum becomes more acid A reverse migration takes place as the reaction becomes more alkaline At $pH_s = 7.40$ the urate distribution ratio is defined by the relation $\frac{\text{cell urate}}{\text{cell water}} \div \frac{\text{serum urate}}{\text{serum water}}$ is approximately 0.60 (Fig. 4) If blood to which urate is added is oxygenated or reduced the urate ratio changes in a manner similar to the chloride and bicarbonate ratios

Solubility of Urate in Serum of Gouty Patients

The significance of an increased concentration of serum urate and its value in the diagnosis of gouty arthritis is not as widely appreciated as is justified from experimental evidence The level of serum urate in gouty patients is definitely above the range for normals a phenomenon manifest by no other arthritic condition and few other morbid states There are innumerable observations in the literature[5] [illegible] which support this statement but unfortunately almost a like number which appear to refute it Garrod's original observation of the increased content of urate in gouty patients was made unwittingly on serum although the *thread was placed in the whole blood phase* The data which we wish to present in confirmation of the significance of the urate level were obtained from the records of 100 patients with gout who were seen by us at the Massachusetts General Hospital during the years 1934–1942 The criteria for selection in this series of observations included (a) the satisfactory establishment of a diagnosis of gout and (b) a periodic follow up The concentration of urate was determined in the serum phase only two or more times in each patient A total of more than 900 *determinations* were done the average number of determinations per patient therefore was approximately 9 The blood for serum determinations was obtained shortly before attacks of acute arthritis during attacks shortly after attacks months after subsidence of any symptoms and during the persistence of low grade symptoms from chronic gouty arthritis Irrespective of the presence of acute articular symptoms irrespective of the duration of the disease and irrespective of the particular type of treatment recommended the serum uric acid was above 6.0 mgm per 100 c c in approximately 98 per cent of the total number of *determinations* The values *ranged from* 5.7 *to* 16.2 mgm per 100 c c of serum The average was 8.8 mgm per 100 c c

More than 400 non gouty individuals were studied as a control series for these observations Many were patients with rheumatoid arthritis or degenerative joint disease others were hospital patients who com

substances which are precursors of exogenous urate. The sources of purine in foodstuffs are those substances which contain a large amount of nuclear material such as liver, kidney, thymus, pancreas, sardines and anchovies. Horbaczewski[73] first showed that their ingestion caused an increased excretion of urinary uric acid. Kruger and Schmid[80] found a similar effect following the ingestion of guanine and adenine.

During the digestion of nucleoproteins the protein fraction is split off by hydrolysis under the influence of gastrointestinal enzymes and leaves nucleic acid. The nucleins are broken down further in the small intestine into nucleotides which in turn yield phosphates and nucleosides.[84] Nucleosides contain one molecule of base and one molecule of sugar. Nucleosides and nucleotides are absorbed from the intestinal tract and eventually are split into purine and pyrimidin bases in the tissues. Thymine, cytosin and uracil are the pyrimidin bases in the nucleoproteins which form urea as the nitrogenous end product. On the other hand adenine and guanine, the purine bases, are deaminized and oxidized to form hypoxanthine and uric acid. It is apparent that neither proteins nor pyrimidin bases of the nucleoproteins contribute to the formation of uric acid in man.

Solubility of Urate in Blood

The maximum solubility of sodium urate in distilled water is approximately 100 mgm. per 100 c.c.[58] The solubility in blood is much less due to the great amount of sodium and other ions normally present.[11] Cudzent[59] obtained a final solubility in serum equivalent to 8.3 mgm. of urate per 100 c.c., while Bechold and Ziegler[7] obtained solubilities over 20 mgm. per 100 c.c. The maximum solubility was obtained after the salt was allowed to remain in equilibrium with the serum for more than a week. Clinical observations on gouty patients show that the maximum solubility observed by Bechold and Ziegler may be approached. Concentrations greater than 10 mgm. per 100 c.c. frequently are encountered and a few patients will have a serum concentration as high as 15 mgm. If uric acid is added in vitro to gouty serum, total concentrations as great as 25 mgm. per 100 c.c. may be obtained within a few hours.[149]

When urate is added to whole blood, it distributes itself between serum and cells in the same proportion as the naturally occurring urate.[149] The distribution agrees approximately with the Gibbs-Donnan law of equilibrium as applied to blood by Van Slyke and associates. There is a migration of urate ions from the serum to the cells as the reaction of the

plained of no joint symptoms still others were patients who had few complaints and were not believed to be suffering from any serious malady More than 96 per cent of the group had a serum uric acid less than 6 0 mgm per 100 c c The average was 4 1 mgm less than half of the average value for the gouty patients The observations permit only one conclusion to be drawn patients with gout who were diagnosed and treated by us had a concentration of serum urate greater than 6 0 mgm per 100 c c a concentration which persisted throughout the period that they were under observation

In order to further test the validity of the contention pertaining to the level of serum urate in gouty patients we were given an unusual opportunity to study a group of patients in the clinic of Dr A Cohen in Philadelphia A group of patients thought to be suffering from gout was assembled by him at one time from the police and fire fighting forces in that city The clinical diagnosis of gout was confirmed tentatively by us in all of the patients Sera for urate concentration and for complete acid base balance were obtained from a total of 33 The data are given in Table I Inspection shows that in all except one patient the concentration of urate was greater than 5 9 mgm per 100 c c The values were 6 0 mgm or greater in all but 3 Even these patients had had at other times according to Cohen concentrations greater than 6 0 mgm

The failure of some physicians to have faith in the diagnostic significance of the serum urate level in gouty patients may be attributed to the selection of whole blood[70, 5, 139] in preference to serum or plasma Whole blood is less reliable because of the concentration of interfering substances in the red cells Since most procedures embody the development of color for the determination of urate any substance which complicates color development partially invalidates the final result Some substances which occur naturally in red cells inhibit color development other substances may be present which enhance color development Whichever may be operating the presence of all intracellular substances should be avoided by the employment of serum or plasma It must be admitted however that some laboratories[111] which have used serum instead of whole blood have found values rather consistently below 6 mgm per 100 c c in patients with gout We are unable to explain this discrepancy

Blauch and Koch[10] recently have described a procedure for determination of uric acid in blood which makes use of the enzyme uricase Values are reported for whole blood rather than serum Uric acid content in whole blood of normals ranged from 1 0 to 3 8 per 100 c c The

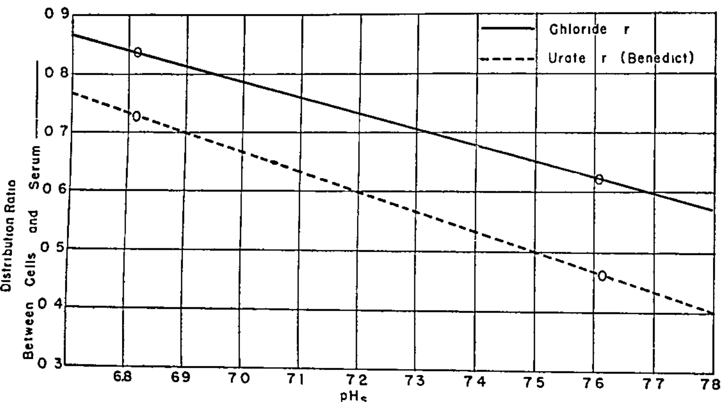


FIG 4 Distribution ratio between serum and cells of chloride and urate as a function of pH_e

plained of no joint symptoms; still others were patients who had few complaints and were not believed to be suffering from any serious malady. More than 96 per cent of the group had a serum uric acid less than 6.0 mgm. per 100 c.c. The average was 4.1 mgm., less than half of the average value for the gouty patients. The observations permit only one conclusion to be drawn: patients with gout who were diagnosed and treated by us had a concentration of serum urate greater than 6.0 mgm. per 100 c.c., a concentration which persisted throughout the period that they were under observation.

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The failure of some physicians to have faith in the diagnostic significance of the serum urate level in gouty patients may be attributed to the selection of whole blood[9, 75, 138] in preference to serum or plasma. Whole blood is less reliable because of the concentration of interfering substances in the red cells. Since most procedures embody the development of color for the determination of urate, any substance which complicates color development partially invalidates the final result. Some substances which occur naturally in red cells inhibit color development; other substances may be present which enhance color development. Whichever may be operating, the presence of all intracellular substances should be avoided by the employment of serum or plasma. It must be admitted, however, that some laboratories[111] which have used serum instead of whole blood have found values rather consistently below 6 mgm. per 100 c.c. in patients with gout. We are unable to explain this discrepancy.

Blauch and Koch[10] recently have described a procedure for determination of uric acid in blood which makes use of the enzyme uricase. Values are reported for whole blood rather than serum. Uric acid content in whole blood of normals ranged from 1.0 to 3.8 per 100 c.c. The

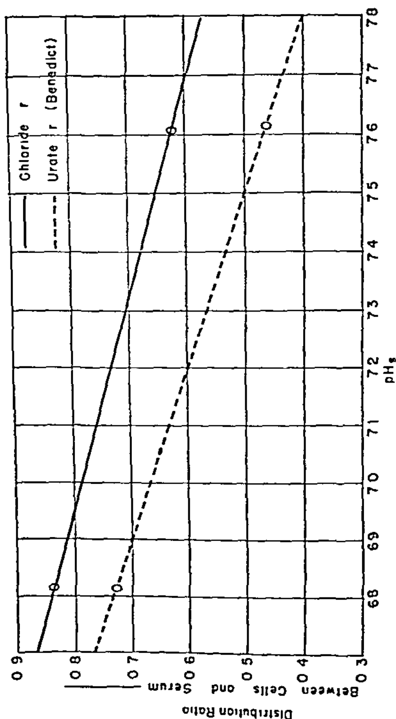


Fig. 4 Distribution ratios between serum and cells of chloride and urate as a function of pH

non-uric acid color value averaged 1.0 mgm. The procedure is laborious and requires great skill. Further studies should be done on this method using serum as well as whole blood as it may explain some of the discrepancies obtained between different laboratories.

Solubility of Urate in Bladder Urine

The solubility of urate in urine in vitro is determined by several factors among which are the concentration of hydrogen ions and the concentration of sodium ions. Within the physiological range of hydrogen ion concentration the more alkaline the urine the greater the solubility of urate. This effect is similar to that observed for solubility in serum. At a constant pH the presence of sodium ions depresses urate solubility. Peters and Van Slyke[11] have calculated that approximately 100 mgm. of uric acid would be held in solution if there were just enough sodium ions present to form a saturated solution of sodium urate at pH = 6.9. Greater amounts at pH values above 6.9 could exist only in supersaturated or colloidal forms. The experimental observations on gouty subjects agree with the theoretical calculations. A maximum solubility of slightly more than 100 mgm. per 100 c.c. of urine has been observed in several gouty subjects[130].

The solubility of urate in vivo, i.e., in bladder urine, is determined by the factors mentioned above but also by the efficiency of the kidneys and the total daily excretion of urate. Urate concentration data are most reliable if endogenous urates only are measured. This may be achieved by the use of a low purin diet, a procedure best followed on a special study ward in a hospital. The data for 12 non-gouty patients are given in Table II. All were studied on a low purine diet on the metabolism ward at the Massachusetts General Hospital under controlled conditions. Other indices of renal function are given in addition to the observations of the ability to concentrate urate. The maximum concentration of urate is less than 50 mgm. per 100 c.c. in all except one subject. These observations agree with those of Folin and associates[41], Grafe[56] and Loewenhardt[130]. It is assumed that a normal person on a low purine diet usually is unable to excrete a urine with a urate concentration greater than 50 mgm. per 100 c.c.

A group of gouty patients was studied next. Urate concentration data from 31 patients are given in Table III. The maximum concentrations were obtained from complete 24 hour specimens or from single morning specimens. No attempt was made to collect urine following restriction of fluid for 12 or more hours as is customary during an over-

TABLE I

ACID-BASE BALANCE OF THE SERUM IN 36 PATIENTS WITH GOUT

Patient no	Total fixed base	Sodium	Potassium	Calcium	Magnesium	Chloride	Protein	Urate
	Concentrations are expressed in milliequivalents per liter						gm per 100 cc	mgm per 100 cc
1	151 4	139 0	4 8	5 2	2 7	100 2	7 4	6 9
[illegible]	154 4	141 9	4 6	5 1	3 2	101 7	7 7	10 1
3	153 7	14[illegible] 0	4 5	4 9	2 9	103 1	6 1	8 0
4	151 5	140 1	4 1	5 0	2 5	100 6	7 0	6 2
5	153 1	14[illegible] 1	3 9	4 9	2 6	102 3	7 2	7 6
6	15[illegible] 5	143 0	4 1	5 2	2 7	96 3	7 9	8 0
7	15[illegible] 9	141 1	4 8	5 0	[illegible] 5	101 0	7 8	8 0
8	150 8	139 5	4 4	4 9	2 2	103 8	6 8	8 0
9	155 9	140 8	4 4	5 3	[illegible] 5	101 1	7 3	10 9
10	154 3	141 0	5 1	5 0	3 0	102 1	6 8	8 5
11	154 7	142 7	4 7	4 7	2 6	104 1	7 1	13 5
1[illegible]	153 9	14[illegible] 1	4 6	5 1	2 5	100 8	7 6	10 1
13	15[illegible] 9	14[illegible] 1	4 2	4 9	2 4	103 6	6 6	5 7
14	15[illegible] 0	140 9	4 [illegible]	4 9	2 4	101 2	6 9	10 7
15	15[illegible] 4	141 0	4 3	5 0	2 4	100 8	7 0	10 4
16	15[illegible] 5	139 3	4 5	5 3	2 5	100 4	7 8	12 4
17	155 3	141 5	5 [illegible]	4 9	2 3	103 9	7 2	10 4
18	15[illegible] 0	139 4	4 0	5 2	2 4	101 6	7 3	9 7
19	152 4	138 9	5 2	5 1	2 4	101 4	6 9	5 8
[illegible]0	149 4	135 5	5 6	4 5	2 5	105 2	[illegible] 5	12 4
21	154 4	141 5	4 5	5 2	2 4	100 9	7 3	11 7
[illegible]	153 6	141 6	4 3	5 [illegible]	2 8	102 0	7 1	6 0
[illegible]3	154 8	14[illegible] 0	5 1	4 7	[illegible] 6	107 3	6 7	6 6
[illegible]4	15[illegible] 3	140 [illegible]	4 7	5 0	3 0	99 7	7 2	10 8
[illegible]5	153 7	141 [illegible]	4 6	5 1	[illegible] 5	101 4	6 8	8 6
[illegible]6	15[illegible] 4	140 5	4 7	5 1	[illegible] 5	105 7	7 3	9 1
[illegible]	15[illegible] 6	139 5	4 2	5 0	[illegible] 6	101 4	6 8	8 3
[illegible]8	156 8	143 1	5 5	5 2	[illegible]	105 5	7 3	9 5
[illegible]9	15[illegible] 9	146 2	4 3	5 0	2 6	99 9	6 0	6 4
30	154 1	140 1	4 9	5 [illegible]	2 7	100 9	7 0	9 0
31	155 3	141 5	4 3	4 8	3 4	97 4	7 7	6 7
32	154 0	139 5	4 6	5 0	3 0	101 8	7 3	10 2
33	153 8	140 1	4 5	4 8	[illegible] 6	102 6	7 2	7 4
34	154 0	140 0	5 0	5 0	3 1	101 4	6 1	6 5
35	15[illegible] 8	140 2	4 8	5 4	2 9	104 0	7 4	9 5
36	153 [illegible]	139 0	4 4	5 [illegible]	3 0	99 4	7 7	10 3

TABLE III

MAXIMUM CONCENTRATION OF URATE IN URINE AND OTHER DATA ON RENAL FUNCTION IN 31 PATIENTS WITH GOUT ON A LOW PURINE DIET

Patient no	Age	Duration of symptoms	Urine			Serum urate
			Excretion of phenolsulfonphthalein	Specific gravity	Maximum concentration of urate	
		year	per cent in first 15 min		mgm per 100 c c	mgm per 100 c c
3	55	20	21	1 01(	44	8 8
37	60	5	14	1 014	)	8 6
38	59	3(	8	1 014	0	6 9
39	42	10	2	1 018	21	6 9
40	55	44	21	1 018	45	6 ,
41	59	½	19	1 012	19	7 3
42	45	4	1	1 010	46	6 6
43	1	3	5	1 012	4-	8 0
44	4	2	55	1 014	45	, 9
45	65	40	15	1 01(	49	6 5
46	41	12	2	1 008	38	9
4	35	6	41	1 0	41	8 0
48	)	39	14	1 014	38	7 9
49	65	25	7	1 014	49	11 3
50	5)	43	17	1 018	34	8 0
51	4	5(		1 010	36	11 0
52	66	9	3	1 008	36	6 4
53	80	7	20	1 0 0	49	10 8
54	38	5	18	1 0 0	40	6 8
55	39	6	18	1 0 0	42	8 0
56	4,	33	8	1 013	11	10 9
57	53	5	10	1 0 0	6	6 0
58	59	4	1	1 015	21	(9
59	38	24	11	1 010		11 (
60	48	1(		1 01(	31	10 3
61	5)	1)	1	1 12	4	8
62	74	5(	1	1 013	48	)
(3	(8		0	1 0 (	8	8
64	5	12			38	10 4
65	(,	2	1(	1 0(8	3	9 0
66	34	11	7	1 014	8	6 8
67	59	30	25	1 014	47	10 8

TABLE II

MAXIMUM CONCENTRATION OF URATE IN URINE AND OTHER DATA ON RENAL FUNCTION IN [illegible] PATIENTS WITHOUT GOUT ON A LOW PURINE DIET

Patient	Age	Urine			Serum urate	Diagnosis
		Excretion of phenolsulfonphthalein	Specific gravity	Maximum concentration of urate		
		per cent in first 15 min		mgm per 100 c c	mgm per 100 c c	
A	[illegible]	45	1 022	28	2 5	Hypertension
			1 033	31	3 4	
B	4		1 022	44	4 1	Normal
C	18	0	1 018	27	11 8	Congenital heart disease
D	9		1 0 4	26	3 7	Normal
E	3	3	1 0 1	49		Raynaud's disease
F	32	20	1 004	43	3 0	Chronic nephritis
G	18	26	1 030	48	4 [illegible]	Epilepsy
H	38		1 0 4	24	3 4	Normal
I	49	40	1 0 [illegible]	40	3 0	Normal
J	39		1 0 8	47	3 1	Pemphigus
K	24		1 028	24		Normal
L	38	39	1 024	74	3 8	Normal

night concentration test The urate concentration data are similar to those for non gouty subjects in that none of the gouty patients was able to concentrate urate above 50 mgm per 100 c c Many of the subjects showed evidence of renal impairment by all of the clinical tests for renal function that were performed These data may be interpreted as representative for the average gouty patient with some degree of renal insufficiency

Finally there is a certain percentage of gouty patients who are able to concentrate urate above 50 mgm per 100 c c We have encountered 11 such patients in our experience This number comprises approximately 25 per cent of those whose urate concentrating ability has been investigated Folin and associates[11] have reported 2 gouty patients with a similar high concentrating ability The observations on 10 of our subjects are given in Table IV None of the specimens was collected during an acute attack of gout or following cinchophen ingestion since

TABLE III

MAXIMUM CONCENTRATION OF URATE IN URINE AND OTHER DATA ON RENAL FUNCTION IN 31 PATIENTS WITH GOUT ON A LOW PURINE DIET

Patient no	Age	Duration of symptoms	Urine			Serum urate
			Excretion of phenolsulfonphthalein	Specific gravity	Maximum concentration of urate	
		years	per cent in first 15 min		mgm per 100 c c	mgm per 100 c c
3[illegible]	55	0	21	1 016	44	8 8
37	60	25	14	1 014	[illegible]	8 6
38	59	3[illegible]	8	1 014	0	6 9
39	42	10	22	1 018	[illegible]1	6 9
40	55	44	21	1 018	45	6
41	59	[illegible]	19	1 012	19	7 3
4[illegible]	45	4	1	1 010	4[illegible]	6 6
43	[illegible]1	3	5	1 01	42	8 0
44	47	2	55	1 014	45	7 9
45	65	40	15	1 016	49	6 5
46	41	1	2	1 008	38	7 9
47	35	[illegible]	41	1 0	41	8 0
48	[illegible]9	3[illegible]	14	1 014	38	7 9
49	65	25	7	1 014	49	11 3
50	5[illegible]	43	1[illegible]	1 018	34	8 0
51	[illegible]4	5[illegible]		1 010	36	11 0
52	66	9	3	1 008	3[illegible]	6 4
53	80	7	20	1 0 0	49	10 8
54	38	5	18	1 0 0	40	6 8
55	39	[illegible]	18	1 0 0	4	8 0
56	47	33	8	1 013	11	10 9
57	53	5	10	1 0 0	2[illegible]	[illegible] 0
58	59	4	1	1 015	1	6 9
59	38	4	11	1 010	25	11 6
60	48	1[illegible]		1 01[illegible]	31	10
61	59	10	1	1 01	4	8 [illegible]
6[illegible]	74	5[illegible]	1[illegible]	1 013	48	[illegible]
63	[illegible]8	2		1 0[illegible]	8	8 [illegible]
64	5	1			38	10 4
[illegible]5	6[illegible]		1[illegible]	1 0[illegible]8	3[illegible]	9 0
6[illegible]	34	11	7	1 014	8	6 8
67	59	30	25	1 014	47	10 8

TABLE IV

MAXIMUM CONCENTRATION OF URATE IN URINE AND OTHER DATA ON RENAL FUNCTION IN 10 PATIENTS WITH GOUT ON A LOW PURINE DIET

Patient no	Age	Duration of symptoms	Urine: Excretion of phenolsulfonphthalein	Urine: Specific gravity	Urine: Maximum concentration of urate	Serum urate
		years	per cent in first 15 min		mgm per 100 cc	mgm per 100 cc
[illegible]8	3	25	19	1 0[illegible]4	87	[illegible] 7
	4	[illegible]	18	1 01[illegible]	10	8 1
[illegible]	3[illegible]	14	6		85	8 5
70	38	3	34	1 024	[illegible]6	9 2
[illegible]1	48	18	3[illegible]	1 016	[illegible]8	8 2
[illegible]	3[illegible]	1	2[illegible]	1 0[illegible]6	10[illegible]	9 3
73	43	[illegible]	30	1 0[illegible]4	[illegible]9	6 8
[illegible]4	5	19	33	1 01[illegible]	83	11 8
	8		17	1 012	82	
[illegible]	3[illegible]	3	38	1 0[illegible]0	73	8 1
[illegible]		5	33	1 014	93	10 0
[illegible]	44		28	1 0	80	7 0

an abnormal augmentation of urate concentration may be associated with other phenomena Three of our patients were studied more than once on the metabolism ward and the ability to concentrate above 75 mgm was checked There are 3 noteworthy differences between the gouty patients who are able to concentrate above 50 mgm and those who are not able to do so The average age of the smaller group is nearly 20 years less than the group which comprises Table III Several of the patients in the smaller group were observed to excrete considerably more than 300 mgm of urate daily on a low purine diet This phenomenon was observed in only one patient in Table III Lastly the incidence of renal impairment is considerably greater in the larger group

In Table V are presented data from the eleventh patient whose ability to concentrate urate was studied in casual specimens as well as during a series of overnight concentration tests The ability to concentrate urate above 75 mgm was a constant finding during each concentration test in contrast to lower concentrations in most casual specimens It is believed that if urate concentrating ability were determined in all

TABLE V

MAXIMUM CONCENTRATION OF URATE IN URINE AND OTHER DATA ON RENAL FUNCTION IN GOUTY PATIENT NO. 8 ON A LOW PURINE DIET

Date	Urine: Specific gravity	Urine: Maximum concentration of urate	Serum urate
		mgm per 100 c c	mgm per 100 c c
February 1935	1.001	130	6
October 1936	1.005	10	10
February 1937	1.019	145	
May 193[illegible]	1.00[illegible]	24	14
January 1939		81	8.[illegible]
May 1941	1.009	10	
February 194[illegible]	1.013	6	7.8
April 16 1942	1.01[illegible]	4	11.6
April 2[illegible] 194[illegible]		10	
April [illegible]6 194[illegible]		9	
May 3 194[illegible]		[illegible]	
May 9 1942		5	11.4

gouty patients following restriction of fluid values above 50 mgm would be observed more frequently.

The conclusion is unavoidable that on a low purine intake the ability of gouty persons to concentrate urinary urate is not unlike that of normal persons. Patients with moderate or serious impairment of renal function are unable to increase urate concentration above 50 mgm per 100 c c. Patients with kidneys that have escaped damage may concentrate above 50 mgm at times. Those who excrete large quantities of urate are able to concentrate without difficulty. In others a restriction of fluid intake for 12 or more hours will bring out the latent ability. The only discrepancy between gouty and non-gouty subjects is a higher value in gouty persons for the ratio serum urate concentration : urine urate concentration. Thannhauser has attributed great significance to this difference and believes that gouty patients have a selective constitutional inferiority of the kidney in regard to ability to concentrate urate. The increased level of serum urate in gouty patients is believed by him to be a direct effect of this differential dysfunction.

Solubility of Urate in Other Body Fluids

The concentration of urate in most body fluids is similar to that in serum[5, 11, 15] This applies to pericardial pleural synovial peritoneal and edema fluid Bauer[5] analyzed the synovial fluid from 5 gouty patients and we have analyzed the fluid from a similar number The agreement between fluid and serum in regard to urate concentration is satisfactory

Spinal fluid is the only media which has been analyzed that has a somewhat lower concentration than serum Reiche[15] analyzed the spinal

TABLE VI

CONCENTRATION OF URATE AND NONPROTEIN NITROGEN IN SERUM AND SPINAL FLUID IN 12 PATIENTS WITH GOUT

Patient no	Urate concentration		Nonprotein nitrogen concentration	
	mgm per 100 c c		mgm per 100 c c	
	Serum	Spinal fluid	Serum	Spinal fluid
42	6 9	1 7	35	29
43	7 9	2 4	36	25
44	7 7	2 6	33	21
46	7 9	1 6	65	46
48	6 5	2 0	32	18
49	6 8	0 9	38	2
54	8 0	2 1	33	24
61	7 7	1 5		
72	8 4	1 2		
78	7 1	1 6	33	19
82	6 3	4	27	17
83	6 4	1 4	23	18

fluid in more than 100 non gouty subjects and found the average concentration of urate to be approximately one third that of serum The serum and spinal fluid data from twelve patients with gout seen by us are presented in Table VI These observations made by us are similar to those which were made by Reiche The concentration of nonprotein nitrogen in the spinal fluid in contrast to the low content of urate was only slightly below that of serum

Renal Exchange of Urate

The concentration of urate in glomerular filtrate which is assumed to be equivalent to that in serum and the concentration of urate in bladder urine which is several times that in serum have been discussed There has been no treatment however of the mechanism whereby the kidney removes water and urate from glomerular filtrate and at the same time excretes a urine of high urate content A satisfactory approach to this problem has not been possible until recently because of the lack of a suitable technique with which to measure rate of formation of glomerular filtrate The researches of Smith and associates[14] have now filled this void Rate of formation of glomerular filtrate may be measured by the clearance of inulin or mannitol starchlike polymers A normal person with a surface area of 1 72 square meters forms approximately 125 c c of glomerular filtrate per minute as measured by these procedures Such an amount seems disproportionately large when considered in relation to the small amount of bladder urine formed in the same period of time The disposition of glomerular filtrate is a function of the tubular epithelium and all but 1 or 2 per cent of the fluid is reabsorbed as it flows through the tubules on its way to the bladder This seemingly small percentage of residual filtrate is sufficient to account for the formation of approximately 2 liters of bladder urine daily

The concentration of most constituents in glomerular filtrate including urate *is similar to their concentration in a protein free filtrate* of plasma Bladder urine would have the same concentration of constituents also were it not for a complicated process of selective reabsorption by the tubules Only one half of the urea present in glomerular filtrate is reabsorbed the remainder is excreted The clearance of urea therefore is computed as approximately one half that of inulin or 60 c c per minute It should be stressed that the clearance of any substance by the kidney is calculated as the volume of plasma needed to carry the quantity of the substance excreted per minute The clearance is independent of the volume of glomerular filtrate reabsorbed by the tubules or excreted into the bladder The clearance of urea is greater than that of most naturally occurring constituents of the body Thus the clearance of sodium and chloride is equivalent to only a few c c of plasma per minute Urate occupies an intermediary position Slightly more than 90 per cent of urate in glomerular filtrate is reabsorbed the remainder is excreted The clearance of urate therefore in a normal person is approximately 8 per cent of 125 c c or 10 c c per minute

The clearance of urate implies that this volume of plasma must have participated in renal activity to provide for the excretion into the bladder of the quantity of urate recovered. This theory of the renal excretion in man postulates that urate, as other filtrable substances, is not excreted by the tubules from the surrounding capillary network. It is noteworthy that the clearance of urea, the end product of nitrogen metabolism, is several fold greater than the clearance of urate.

Precise measurements of urate clearance have been made by few investigators. Brøchner-Mortensen[11] studied this function in normal persons and observed a mean value of approximately 7 c.c. of plasma per minute. This observation has been confirmed by us for normal persons and extended to include gouty subjects. Many of the data are presented in Table VII. Urate clearance of gouty patients in this series is approximately 10 c.c. per minute. The mean is only slightly below that for non-gouty controls.[23] In addition to determining urate clearance, glomerular filtration rate (inulin or mannitol clearance) was determined concomitantly. The simultaneous estimation of both functions is expedient, since urate clearance gives most information when it is related to glomerular filtration rate. An average glomerular filtration rate of 125 c.c. per minute may be assumed in normal persons without introducing a significant error. Such an assumption is hazardous, however, in gouty patients, since many show evidence of renal impairment with a reduction in filtration rate as great as 50 or 75 per cent (Table VII).

If data on rate of formation of glomerular filtrate are available, the per cent reabsorption of urate by the tubules may be calculated from the formula $1 - \frac{\text{urate clearance}}{\text{glomerular filtration rate}} \times 100$. This value, per cent reabsorption of urate, is most pertinent. Gouty patients and non-gouty subjects with a glomerular filtration rate greater than 100 c.c. per minute and a urate clearance of approximately 10 c.c. per minute have a per cent reabsorption value of approximately 90 per cent. Urate clearance tends to be maintained at the expense of per cent reabsorption as glomerular filtration rate is impaired in gouty patients by progressive damage. Per cent reabsorption may be reduced as much as 30 per cent with severe reduction of kidney function.

In Figure 5 are shown urate clearance data for 28 gouty subjects and 55 non-gouty controls. The distribution of the data is similar for both groups. The interpretation of these findings is thought to furnish additional support to our contention that gouty kidneys show no differential inability of the kidneys to clear urate. Only in such patients

TABLE VII

RENAL FUNCTION OBSERVATIONS ON PATIENTS WITH GOUT

Patient no.	Age	Duration of symptoms	Glomerular filtration	Renal blood flow	Diodrast Tm	Urate clearance	Excretion of phenolsulfonphthalein	Specific gravity	Serum nonprotein nitrogen
		year	cc per min		mgm per min	cc of plasma per min	per cent in first 15 min		mgm per 100 cc
3	43		130			(	30	1 0 4	8
0	38	3	11(			9	34	1 0	3
)	47	1	10(				4	1 0	50
(	59	30	10			10	2(	1 014	3)
(	(	5	100			8	8	1 014	28
80	41	3	100				1(	1 015	8
	53	5	95			8	1)	1 02)	34
(1	50	18	95				3)	1 0	5
4	35	6	)5			9	41	1 0	8
(8	4	2(	74			11	18	1 016	5
0	59	43	73				1	1 01(	3
51	((	12	(2			1)	28	1 013	8
(4	5	1	1			(	18	1 018	28
))	3)	(	69			8	(	1 010	30
8	31	10	(8			(	2(	1 009	8
8	34	13	(4	3))	3)	)	18	1 010	30
65	6(		6			5	1(	1 01(	28
48	81	3)	(			5	14	1 009	(
(	60	5	62	340	4		14	1 014	8
3)	42	10	60	350	3)	9	21	1 018	31
41	59	½	58	350	34	8	19	1 012	3
49	65	5	5(			8		1 (14	32
38	5)	3(	36	13)	5	)	8	1 014	34
43	71	3	31			8	5	1 01	4(
4(	41	1	9			5		1 008	()
52	(	)	5			)	3	1 008	44
5(	4	33	1			4	8	1 (13	6(
Average Range for Normal									
			100	(00	45	(	5	1 0 0	20
			140	00	5	12	40		35

The clearance of urate implies that this volume of plasma must have participated in renal activity to provide for the excretion into the bladder of the quantity of urate recovered. This theory of the renal excretion in man postulates that urate, as other filtrable substances, is not excreted by the tubules from the surrounding capillary network. It is noteworthy that the clearance of urea, the end product of nitrogen metabolism, is several fold greater than the clearance of urate.

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If data on rate of formation of glomerular filtrate are available, the per cent reabsorption of urate by the tubules may be calculated from the formula $1 - \frac{\text{urate clearance}}{\text{glomerular filtration rate}} \times 100$. This value, per cent reabsorption of urate, is most pertinent. Gouty patients and non-gouty subjects with a glomerular filtration rate greater than 100 c.c. per minute and a urate clearance of approximately 10 c.c. per minute have a per cent reabsorption value of approximately 90 per cent. Urate clearance tends to be maintained at the expense of per cent reabsorption as glomerular filtration rate is impaired in gouty patients by progressive damage. Per cent reabsorption may be reduced as much as 30 per cent with severe reduction of kidney function.

In Figure 5 are shown urate clearance data for 28 gouty subjects and 55 non-gouty controls. The distribution of the data is similar for both groups. The interpretation of these findings is thought to furnish additional support to our contention that gouty kidneys show no differential inability of the kidneys to clear urate. Only in such patients

as show serious depression in glomerular filtration rate 35 c.c. per minute or less is retention of urate from a kidney disturbance manifest

The excretion of urate by the kidney may be modified by the action of several drugs Salicylate was the first drug to increase urate excretion that was discovered This observation was made by See in 1875[110] It was confirmed by Campbell two years later[13] who made the additional observation that colchicine had no effect upon urate excretion It has been shown in recent years that cinchophen has an effect similar to salicylate[115 184] There are no experimental data which suggest that either salicylate or cinchophen augment urate output by altering the intermediary metabolism of purines[48] Neither is there any appreciable increase in amount of urate filtered by the glomerulus nor any change in permeability of the glomerular membrane for passage of urate The site of action most likely is in the renal tubules[64] The action of cinchophen probably is a mildly toxic one toward the tubular cells similar to the toxicity displayed toward liver parenchymal cells The mechanism of salicylate diuresis presumably is different Tubular cells have a particular affinity for benzoic acid ring compounds[141] and become actively concerned in removing them from the blood following their ingestion The process requires considerable cellular energy and when the tubules are busily engaged in the excretion of salicylate they are unable to give proper attention to reabsorption of urate An increased excretion of urate with a diminished percentile reabsorption follows and is maintained so long as salicylate is present in circulating blood

Application of the clearance technique to the study of the action of drugs has strengthened the validity of the assumptions regarding urate exchange in gouty persons Cinchophen[3] and salicylate have been shown to increase urate clearance two or three fold while colchicine has no demonstrable effect (Table VIII) There is little difference in regard to effect upon urate clearance between cinchophen and salicylate when given in therapeutic doses Salyrgan has a very remarkable effect upon urate clearance This value may be increased four or five fold following the intravenous injection of 2 c c of the substance The action of salyrgan is similar to that postulated for cinchophen The tubular epithelium is insulted temporarily and normal reabsorption of urate is prevented as is the reabsorption of other electrolytes particularly sodium chloride and water There is no evidence which indicates that salyrgan produces its diuretic effect by an increase of rate of formation of glomerular filtrate

The maximum effect upon urate clearance which we were able to

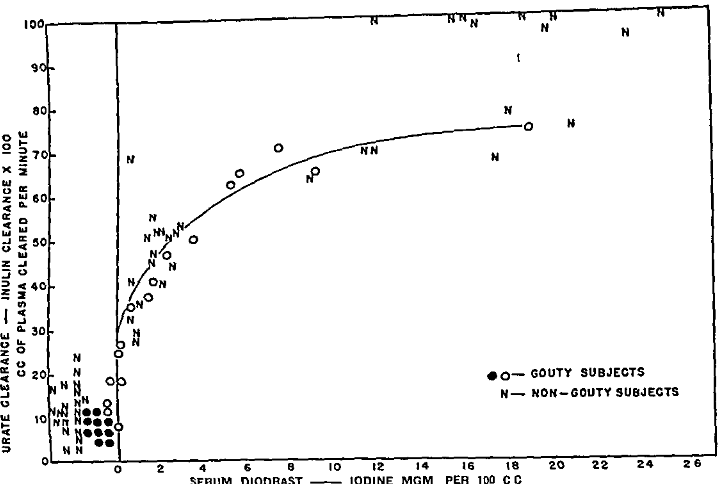


FIG 5 Urate clearance as a function of inulin clearance (glomerular filtration rate) in gouty and non gouty subjects The data between the zero lines are basal controls The data to the right of the second zero line were obtained following intravenous administration of diodrast It is concluded that there is no significant difference between gouty and non gouty subjects in the ability of the kidney to clear urate

produce by any mechanism followed the intravenous administration of diodrast (3 5 diiodo 4 pyridon N acetic acid diethanolamine) The effect may be demonstrated in either gouty or non gouty subjects At low concentrations of diodrast 1 mgm per 100 c c of plasma the increase in urate clearance is two or three fold normal (Fig 5) At high plasma diodrast levels 25 to 40 mgm per 100 c c urate clearance approaches glomerular filtration rate and reabsorption is minimal or absent The reabsorption of other substances which were measured sodium chloride potassium and phosphate is not altered by either high or low concentrations of diodrast Diodrast is excreted in large part by tubular cells as is salicylate and little or no urate is reabsorbed during periods of maximal excretory activity

Other substances which have been tested in regard to an effect upon urate clearance include glucose inulin mannitol and phenol red (Table VIII) Some of these substances are handled by the tubules others are excreted solely by glomerular activity Glucose at high plasma levels has an effect upon urate clearance that is almost as great as diodrast When the plasma level of glucose exceeds 400 mgm per 100 c c achieved by intravenous administration of 100 grams or more of glucose only small quantities of urate are reabsorbed Since only a portion of the glucose present in glomerular filtrate is excreted in the urine the remainder is reabsorbed by the tubules and takes precedence over reabsorption of urate The depression in urate reabsorption from a purely diuretic effect exerted by glucose has been excluded

Inulin and mannitol at similarly high plasma levels have as great a diuretic effect as glucose Neither mannitol nor inulin however at high or low plasma levels influence urate clearance since they are excreted solely by glomerular activity and the tubular cells are not concerned with reabsorption of any portion which appears in glomerular filtrate Phenol red is excreted largely by the tubules as is diodrast and at plasma levels of approximately 10 mgm per 100 c c the effect upon urate clearance is similar to that of salyrgan

Other substances which are known to be excreted by the renal tubules creatinine sodium hippurate and p amino hippurate have no effect upon urate clearance either at high or low plasma levels Pitressin a substance which promotes increased reabsorption of water and salt by the renal tubules has no effect upon urate reabsorption Aminophylline[9] and epinephrine[56] are reported to produce an increased excretion of urate These drugs have not been studied with the clearance technique

TABLE VIII

ACTION OF DRUGS UPON URATE CLEARANCE IN GOUTY AND NON-GOUTY PATIENTS

Experimental Substance: Description	Experimental Substance: Serum concentration	Serum urate	Urate clearance	Urate reabsorption	Glomerular filtration rate	Comments
	mgm per 100 c c	mgm per 100 c c	c c of plasma cleared per min	per cent	c c of per min	
Diodrast (Diiodopyridon acetic acid diethanolamine)	46	6.1	49	-	50	
Glucose	440	3.1	56	13	63	Patient suffering from schizophrenia
Sodium salicylate		8.8	35	48	67	5 grams of sodium salicylate given orally six hours before test
Phenol red		6.9	8	51	57	
Salyrgan		11.0	33	52	69	[illegible] c c salyrgan given intravenously two hours before test
Diodrast	1	10.[illegible]	30	62	80	
Cinchophen		6.0	18	76	74	3 grams of cinchophen given before test
Sodium hippurate		9.5	9	88	75	8 grams of sodium hippurate given intravenously during test
p-amino hippurate	14	11.4	10	87	70	
Creatinine	7.4	11	6	91	67	
Colchicine		[illegible]	11	86	80	5 mgm colchicine given orally six hours before test
Mannitol	440	8.6	8	89	72	
Inulin	128	10.7	14	85	92	
Pitressin		6.0	10	89	90	Diabetes insipidus 1.0 c c pitressin given intravenously during test

produce by any mechanism followed the intravenous administration of diodrast (3 5 diiodo 4 pyridon N acetic acid diethanolamine) The ef fect may be demonstrated in either gouty or non gouty subjects At low concentrations of diodrast 1 mgm per 100 c c of plasma the in crease in urate clearance is two or three fold normal (Fig 5) At high plasma diodrast levels 25 to 40 mgm per 100 c c urate clearance ap proaches glomerular filtration rate and reabsorption is minimal or absent The reabsorption of other substances which were measured sodium chloride potassium and phosphate is not altered by either high or low concentrations of diodrast Diodrast is excreted in large part by tubu lar cells as is salicylate and little or no urate is reabsorbed during periods of maximal excretory activity

Other substances which have been tested in regard to an effect upon urate clearance include glucose inulin mannitol and phenol red (Table VIII) Some of these substances are handled by the tubules others are excreted solely by glomerular activity Glucose at high plasma levels has an effect upon urate clearance that is almost as great as diodrast When the plasma level of glucose exceeds 400 mgm per 100 c c achieved by intravenous administration of 100 grams or more of glucose only small quantities of urate are reabsorbed Since only a portion of the glucose present in glomerular filtrate is excreted in the urine the remainder is reabsorbed by the tubules and takes pre cedence over reabsorption of urate The depression in urate reab sorption from a purely diuretic effect exerted by glucose has been excluded

Inulin and mannitol at similarly high plasma levels have as great a diuretic effect as glucose Neither mannitol nor inulin however at high or low plasma levels influence urate clearance since they are excreted solely by glomerular activity and the tubular cells are not concerned with reabsorption of any portion which appears in glomerular filtrate Phenol red is excreted largely by the tubules as is diodrast and at plasma levels of approximately 10 mgm per 100 c c the effect upon urate clearance is similar to that of salyrgan

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The Gout Cycle

An alteration in the concentration of certain constituents of body fluids during an acute attack of gout has been known for many years. A diminished excretion of urate before the onset of acute articular symptoms and followed by an increased excretion during the attack has been reported by Futcher[46], His[2] and Umber[159]. These observations have been confirmed recently and extended to include other constituents of body fluids and other functions of the body. So constant were the fluctuations in relation to acute attacks and so rhythmic were they in character that the term gout cycle[148] was used to describe them. Our observations were made while the patients were consuming a constant amount of food and fluid daily and while they were confined to the metabolism ward at the Massachusetts General Hospital. A diuresis which began from 24 to 72 hours before the onset of articular symptoms was a frequent observation. It was accompanied by an increased excretion as well as an increased concentration of various urinary constituents but particularly sodium and chloride. The flood of substance reached a peak shortly before or shortly after the onset of joint distress. A retention of these substances by the body occurred late in the attack, and the balance for the complete cycle showed neither a gain nor a loss.

In the prodromal period before the onset of joint symptoms a gain in body weight accompanied the diuresis. It was assumed that conditions being such as they are on a constant metabolic regimen only a significant diminution in insensible water loss could explain the gain in body weight which occurred simultaneously with the diuresis. Subsequent studies on weight change associated with insensible perspiration showed that the paradoxical gain in weight was caused by a decrease in the water loss from insensible perspiration. Furthermore it was shown that cyclic changes in concentration of certain constituents of body fluids in excretion of urates and sodium chloride and in body weight occurred in interval periods unrelated to acute attacks. It is believed now that cyclic changes in the internal environment of the body of gouty patients occur irrespective of the presence or severity of acute joint symptoms.

In a search for an explanation of this cyclic phenomenon a relationship to meteorological factors, i.e. barometric pressure, relative humidity and atmospheric temperature, was considered. A consistent correlation was noted between fluctuations in barometric pressure, insensible weight loss and diuresis[150] when the daily variations in meteorological factors

were charted against the metabolic changes. A drop in the barometric pressure preceded the diuresis which in turn preceded the joint symptoms if an acute attack developed. The temporal relations were maintained between barometric pressure and diuresis in cycles not associated with joint symptoms. These quantitative studies furnish experimental evidence in support of certain clinical observations. There are patients with gout who believe that they can predict an acute attack of arthritis from an increased urinary output[131] gastrointestinal distress[95] suppression of sweating or a gain in body weight. Although it is not common for gouty patients to forecast a storm from symptomatic changes in the joints as a patient with rheumatoid arthritis frequently does a statement by Scudamore[173] is pertinent: "I know several gouty patients whose sensibility to the immediate influence of the east wind is almost inevitable." It is recognized that an east wind generally accompanies a falling barometric pressure and the association of meteorological changes and symptoms of gout may be greater than is now appreciated.

Acid Base Constituents of the Serum

Data of the acid base balance of the serum from 33 gouty males have been presented already in Table I. The various clinical stages of gout are represented in the group although none was suffering from acute gouty arthritis at the time the blood was drawn. There is no striking variation from the normal in this series of determinations except as regards urate concentration.

Chemical Analysis of a Tophus

The following quantitative analysis[5] is representative of a desiccated tophus:

Urate	59.7%
Organic Material	27.9%
Sodium Oxide	9.2%
Potassium Oxide	3.0%
Calcium Oxide	0.2%
Magnesium	trace
Iron	trace
Phosphate	trace
Sulphur	trace

Morbid Anatomy

Urate Deposition

The distinguishing pathological feature of gout is the deposition of sodium urate in soft tissues and in bony structures in various regions of the body It is believed by the writer although it has not been proved that deposition of urate in joints probably precedes clinical symptoms of acute gouty arthritis Recurrent deposition of microscopic amounts of urate may continue for years before tophi are demonstrable grossly or on physical examination The word tophus or ' tofus the Greek τοφος was applied to rough crumbling rock the disintegrated volcanic tufa[illegible] It is an appropriately descriptive term

The mechanism responsible for deposition of sodium urate in gouty persons has not been elucidated Undoubtedly it is related to the increased concentration of urate in synovial and other body fluids Precipitation of salts from body fluids is always a potential threat since the maximum solubility of urate is not great The fact that the earlies changes observed at microscopical examination of joints are deposits of urate in the upper layer of cartilage[111, 160] (Fig 6) suggests that urate comes from synovial fluid rather than directly from the capillaries in the bony structures Duckworth[illegible] was the first to demonstrate urate crystals projecting into the matrix of the cartilage (Fig 7) perpendicular to the joint surface This observation together with the finding of a synovitis (Fig 8) convinced Pommer[123] that the initiating process probably was in the joint cavity and that deposits of urate in the cartilage followed Pommer offered no explanation for the cause of the synovitis

Opposed to this theory were the conclusions of Ebstein[33] and Brogsitter[13] who conceived of a reverse path i e urate crystals migrating from the epiphysis to the articular surface A polemic also has been waged over the ability of articular tissue to attract urate Ebstein championed the theory that focal necrosis antedated the precipitation of urate Allbutt[1] influenced by Strangeways[88] was a strong proponent of the necrosis theory Other observers[16, illegible] but particularly Pommer[illegible] who has written an excellent monograph on the pathology of gout are reluctant to accept this explanation We are inclined to agree with Pommer Infiltration of the cartilage with urate is shown in Figures 6 and 7 but there is no demonstrable evidence of necrosis of the cartilage either in the midst of the urate mass or along the outer fringes of the advancing urate border A second argument



Fig 6 Single chondral tophus in metatarsal phalangeal joint of great toe Layer of urate along cartilage margin no foreign body reaction adjacent to urate Most cartilage cells that are visible are essentially normal X ray of a similar chondral tophus shown in Fig 15

against the focal necrosis theory is the unlikelihood of any necrotizing process which is responsible for such widely disseminated trauma developing progressively over a period of so many years

Urate deposits are prone to develop in avascular rather than vascular tissue[160] The common sites are articular cartilage epiphyseal portions of bone synovial membranes bursæ ligaments tendons (Fig 9)

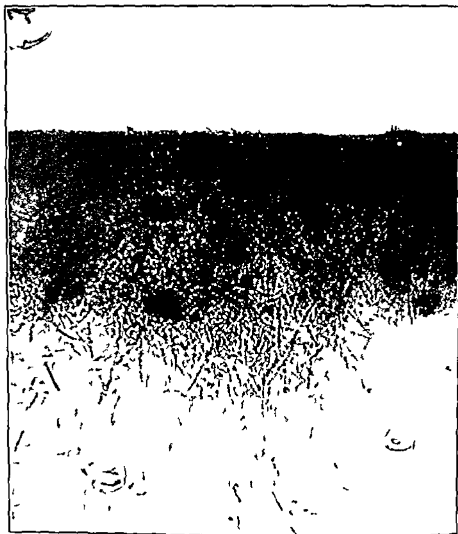


FIG 7 Deposition of urate along margin of cartilage Urate needles are seen penetrating perpendicular to surface invaded cartilage cells appear as black spots no foreign body reaction

and the cartilage supporting the helix of the ear (Fig 10) All of the articular and peri articular structures of several joints may be riddled by urate tophi in advanced cases of gout Soft tissues some distance removed from the aforementioned structures rarely are involved except the kidneys Tophi are conspicuously absent from muscle liver spleen lungs and nervous tissue



Fig 8 Clumps of urat needl in synovia cve ly ng a cart laginous tophu Black area caused by mass of urate in invad d cartilage l s of normal ar hitecture

Articular St uctures

The gross appearance of a gouty joint depends upon the age of the patient and the duration and the severity of the disease A joint in young or middle aged persons which has been the site of only a few acu e attacks of gout may show little except a few microscopic urate deposits The deposits spread over a larger area as the disease progresses and finally the articular cartilage may be covered as completely as an icing covers a cake (Fig 11) There may be lipping and grooving in older persons evidence of degenerative joint di ease In an advanced case of gout irrespective of the age of the patient urate deposits may be inter mingled with pathological changes characteristic of d generative joint

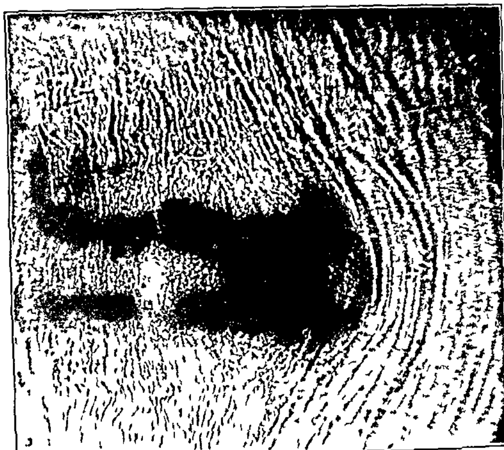


FIG 9 Urate deposit displacing tendon fibers in the Achilles tendon urate needles seen radiating from black area in left hand portion of tophus

disease and in other areas with pathological changes similar to those observed in rheumatoid arthritis This has led some investigators to designate gouty arthritis as a "mixed" type of arthritis[31] The synovial membrane may show few effects of urate invasion or there may be considerable hypertrophy and loss of normal architecture Extensive erosion and destruction of the cartilage may be followed in some instances by fibrous ankylosis (Fig 11) Complete destruction of a joint and replacement by a urate tophus rather than by fibrous tissue is even rarer (Fig 12) The few joints that we have observed at x ray examination that have undergone this series of changes have been surrounded by a thin shell of calcium

Calcium deposits have been noted infrequently in soft tissue following



FIG 10 Lobulated tophus in helix of ear patient No 48

urate deposition (Fig 13) Urate changes in gouty joints are associated in most instances with absorption and not deposition of calcium salts The exostoses (Fig 14) referred to previously as characteristic of degenerative joint disease are associated with calcium deposition but are



Fig 11 Urate depo it covering surface of both cartilages of a joint superficial and deep invasion Urate deposits hown as black areas cartilage replaced by urate and eventually by fibrou tissue in right hand portion of joint

not believed to be an integral part of the pathological structure of gouty joints

The pathological material selected for microscopical examination must be prepared with especial care by a laborious and painstaking technique A non aqueous solution is to be preferred for the fixing of specimens since urates are soluble in water Absolute alcohol serves this purpose best Sections may be stained by one of several procedures[19 1 3 165]

The cartilage cells lose their normal appearance and subsequently are replaced by urate as the invasion from the superficial layers proceeds Gradual progression of urate infiltration causes large portions

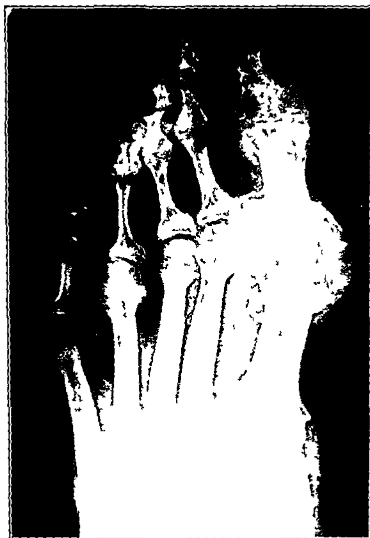


Fig 1 Advanced gouty changes particularly of metatarsal phalangeal and terminal phalangeal joints of great toe Cortex of bone markedly thinned joint margin of bones expanded to twice normal size metatarsal phalangeal joint completely replaced by urate deposits several tophi in fifth toe extensive deposition of urate in subcutaneous spaces patient No 51 female

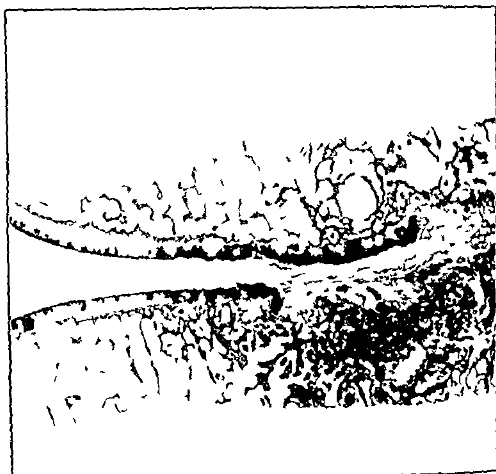


FIG 11 Urate deposits covering surface of both cartilages of a joint superficial and deep invasion Urate deposits shown as black areas cartilage replaced by urate and eventually by fibrous tissue in right hand portion of joint

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Fig 14 New bone formation about metatarsal phalangeal and terminal phalangeal joints of great toe Narrowing of joint space osseous tophi scattered throughout the great toe especially in tarsal metatarsal joint patient No 38



FIG 13 Tophus in olecranon bursa Irregular erosion without invasion of cortex of bone calcification in the tophus probably the result of urate deposition no history of acute bursitis patient No 43

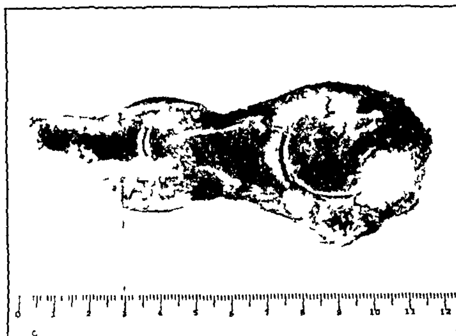


FIG 16 Sagittal section of great toe Extensive urate deposition foot from which toe subsequently was removed is shown in Fig 3 patient No 6

of cartilage to be involved with the development of clefts and irregularities (Fig 6) *Subchondral bony trabeculæ* (Fig 15) medullary spaces capsules ligaments tendons bursæ and other periarticular structures are invaded eventually (Fig 16) Periarticular tophi may show fibroblasts polynuclear cells and giant cells[1-3] interwoven with urate crystals (Fig 17) The tissue cells are crowded as the tophus enlarges and an avascular mass of urate remains following their death The tophus is surrounded by a connective tissue capsule when it reaches a size that is cosmetically unattractive Vascular sclerosis may be apparent in and about tophi

It is not necessary to postulate that urate deposits cause necrosis of bone during or after infiltration of the medullary spaces It is sufficient to assume that urate deposits in apposition to bony trabeculæ inhibit osteoblastic activity and that as bone is resorbed normally it is not replaced in the immediate vicinity of a tophus Since bone is capable of regeneration however it is possible for tophi in bone to be



Fig 15 Chondral and subchondral tophi in great toe Hypertrophic lipping and hallux valgus patient No 6, compare Fig 47

then by the reaction of the joint to this insult This is an ingenious explanation and may be valid for acute attacks which follow joint trauma It does not explain however acute attacks which presumably are incited by non traumatic causes We are inclined to agree with Pommer that the morphological pattern of gouty joints probably is not materially altered during an acute attack

Kidneys

The pathological components of the kidney in gouty persons are constant in regard to the presence of urate but variable in the amount and nature of parenchymal changes The kidneys may be normal in size and weight or they may be small and atrophic and less than one third the normal size The capsules may strip easily or with some difficulty The exposed surfaces show minimal to marked scarring If urate deposition is slight it will be evident only from a gritty sensation with the knife as the kidney is sectioned A careful search with a dissecting microscope should be made if urate crystals are suspected but are not identified grossly Urate deposits are visible readily on the cut surface of the kidney in advanced cases They appear as streaks of white throughout the parenchyma[73] but are most abundant in the medullary regions (Fig 18) The white urate streaks were reported first by de Castelman in 1843 according to Garrod

The lesions are as variegated microscopically (Fig 19) as they are grossly and may simulate chronic glomerular nephritis vascular nephritis pyelonephritis or amyloid nephrosis[97] The glomeruli show partial or complete hyalinization Many glomeruli which apparently have not lost their ability to function show thickening of the intercapillary substance Large and small vessels show proliferation of the intima and narrowing of the lumina The tubules are dilated and loaded with urate crystals and hyaline casts or are atrophied and surrounded by interstitial fibrosis Deposits of urate in the interstitium may invoke a chronic inflammatory reaction with accumulation of lymphocytes and foreign body cells

One patient in our series showed extensive deposits of amyloid between the capillary loops around the afferent arteries and in the intima of the vessels The development of amyloid kidneys followed a long standing but low grade pyelonephritis

There is no satisfactory explanation of the lack of uniformity of the morbid processes The presence of vascular disease in the kidney is not unexpected since patients with gout tend to develop arteriosclerosis



FIG 17 Microscopic section of a tophus removed from olecranon bursa Urate needles interwoven between fibroblasts patient No 53

resolved and replaced by normal bone This series of events probably is unusual and most tophi that develop in bone increase in size rather than decrease

The pathological features give little clue as to the mechanism of an acute attack. Brogsitter[1] believed that a bulging uric acid deposit in an outer layer of cartilage ruptured into the joint space before an acute attack The clinical symptoms of acute gouty arthritis would be caused



Fig 19 Photomicrograph of the medulla of the kidney shown in Fig 18 Several large deposits of urate are evident patient No 43

maximum and removal of water from glomerular filtrate during formation of bladder urine may leave a supersaturated solution of urate in the renal tubules Precipitation from such a solution always is a threat and usually is a fact We have had an opportunity to examine the kidneys of 9 patients with gout in our series Deposition of urate was demonstrated in all

Heart

The heart in gout may be the victim of two processes The coronary vessels share in the generalized arteriosclerosis and frequently become insufficient Coronary occlusion was second to renal insufficiency in incidence as a cause of death in our series of patients The incidence of coronary sclerosis in gouty patients has been partially responsible for the unconfirmed supposition that coronary disease in non gouty persons one aspect of the gouty diathesis Myocardial hypertrophy particularly of the left ventricle is the second cardiac sequela of chronic gout

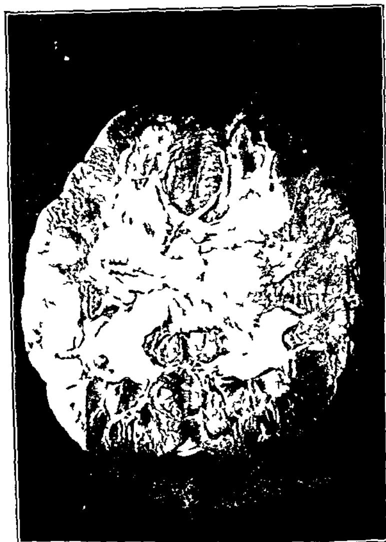


Fig 18 Gross appearance of a gouty kidney White streaks of urate visible throughout the parenchyma patient No 43

throughout the body prematurely The incidence of other types of nephritis may be related to a lower susceptibility of the kidney which in turn is related to the damage from urate deposition in the renal tubules and interstitium

The pathogenesis of urate deposition in the kidney may be interpreted in the light of the physical properties of urate and the exchange of it by this organ The solubility of urate in gouty serum is near the

There is no ready explanation for the discrepancy between European and American data.

Endogenous factors responsible for gout are thought to be intimately concerned with the intermediary metabolism of purine substances and with the urinary excretion of urate. There are three possible metabolic dysfunctions which might lead to an increased concentration of urate in body fluids. These are (1) diminished destruction of urate by the body, (2) diminished excretion by the kidney, and (3) increased formation by the body. Conclusive experimental data in support of each of these hypotheses is lacking. The several theorems supported by evidence or refuted by counterevidence will be presented in the order of increasing probability.

Destruction by the human body of significant quantities of either endogenous or exogenous uric acid has never been proved[15]. The only probable biological mechanism for disruption of urate should utilize the enzyme uricase. The concentration of uricolytic ferments in human tissues, save for the liver and intestines, is very low, which suggests *that man's internal environment was not constructed to destroy uric acid*. The degradation product of uric acid in animals is allantoin, and presumably the action of uricase in man would produce the same end result. However, only a few milligrams of allantoin are excreted by humans daily, and a failure of a supposed uric acid→allantoin oxidation system seems unlikely. The other chemical possibility, uric acid→urea, seems even more remote, as there is no known enzyme capable of initiating this reaction. The destruction of uric acid by humans following the administration of a few hundred milligrams of the material has not been proved. Although Burian and Schur[17] recovered only 50 per cent of the quantity injected, other workers[43, 134] have reported *greater percentile recoveries even up to 100 per cent of the amount given*. Because of the arguments advanced, it seems unlikely that the decreased destruction theory is valid, and other processes must be investigated in the search for a sound explanation of the etiology of gout.

Diminished excretion of urate by the kidneys is the popular current explanation of the increased concentration in body fluids. Garrod was one of the first of the modern physicians to propound this theory. Thannhauser[157], a staunch supporter of it, presumed that a specific impairment of the kidney in regard to excretion of uric acid was responsible without impairment necessarily of other functions. It is agreed by all observers that most gouty subjects in the early years of the disease, particularly those who have the malady in a mild form, have normal renal function as shown by routine clinical tests. Execution of the precise tests for

Etiology

The etiology of gout is not known The theories concerning the cause of the malady however suggest that certain advances have been made already and suggest the possibility of further progress There are at least two accepted facts relative to the disease that are pertinent to the discussion of the etiology (1) The malady is a familial one called by Garrod an inborn error of metabolism (2) An increased concentration of serum urate is the sine qua non of gout The recognition of the familial nature of the malady immediately offers certain clues for investigation This has been discussed under Heredity and certain deductions were made from the finding of an increased content of urate in body fluids of non affected relatives

An increased concentration of serum urate in gouty patients is the counterpart of hyperglycemia in diabetes mellitus and of polyuria in diabetes insipidus Just as hyperglycemia per se is not responsible for many of the serious consequences of diabetes mellitus so hyperuricemia in gout is not the only devil in the disease Hyperuricemia is present in mild as well as in severe cases it may be observed during acute attacks and during symptom free periods Hyperuricemia however would not be an ominous dysfunction were it not for the subsequent deposition of urate in soft tissues and bone An adequate explanation of gout therefore should account for the increased concentration of urate in body fluids and the deposition in tissues

An increased concentration of urate in body fluids of gouty patients might be caused by exogenous factors or by endogenous factors Diet alcoholic beverages a sedentary existence and exposure to lead have been held responsible There is little experimental evidence in support of the first three factors It is more difficult to dismiss lead as an etiological agent Exposure to lead was a popular theory a generation or two ago particularly in England[51] and in Germany[95 97 104 105] Strierlin[146] estimated that 3 per cent of the cases of lead poisoning seen by him suffered from gout as well The association of lead poisoning and gout in the United States on the other hand is rare Aub and associates[1] reported not a single instance of gout developing in a large series of patients afflicted with lead poisoning There is only one instance of recognized lead poisoning in our series of gouty patients This patient (No 58) had severe symptoms of lead intoxication and mild symptoms of gouty arthritis Probably the most reliable index of the association of gout and lead poisoning comes from necropsy material Gudzent[60] discovered 6 cases of lead intoxication in 76 autopsies on gouty patients

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renal function glomerular filtration rate renal blood flow and maximum capacity of the tubules for excretion of diodrast respectively in a small group of gouty patients (Table VII) has led to similar conclusions As acute articular attacks recur and the disease progresses one or more indices of renal efficiency show evidence of deterioration A small amount of albumin in the urine inability to concentrate solids maximally eel indrurii or a decrease in rate of formation of glomerular filtrate may be the first demonstrable sign The persistent appearance of any one of these demeanors is significant and is indicative of irreparable kidney damage Late in the course of renal impairment the specific gravity is fixed excretion of phenolsulphonphthalein dye is delayed markedly and the concentration of nonprotein nitrogen of the serum is increased These are ominous signs The point to be stressed is that kidney function in patients with gout should not be called normal if any of the above mentioned findings are observed Furthermore the kidneys of gouty patients should be tested with as many diverse procedures as possible since they may appear normal if one or two tests only are applied but show evidence of impairment if all of the available tests are used

The various tests have been applied by us to a large number of gouty patients Particular attention in this study was given to the concentration of urate in the urine Thannhauser has shown that gouty patients frequently are unable to concentrate urate above 50 mgm per 100 c c We have confirmed this observation in many patients who show evidence of renal impairment but we have in addition a significant number of gouty patients without demonstrable renal impairment who are able to concentrate urate above 75 mgm We believe that the discrepancies between our data and those in the literature may be understood only if the observations are interpreted relative to the state of the kidneys at the time that their ability to concentrate urate is determined If renal impairment is demonstrated by several of the routine clinical tests for renal function then it is most likely that the subject will be unable to concentrate urates above 50 mgm per 100 c c On the other hand gouty subjects with little or no evidence of renal damage may excrete a urine with a urate concentration above 75 mgm per 100 c c

Urate clearance and urate reabsorption studies confirm the assumption that no differential impairment of the kidney in regard to urate excretion exists There appears to be little difference in regard to renal exchange of urate between gouty and non gouty persons (Fig 5) Furthermore when urate reabsorption is altered by the action of such

substances as diodrast and cinchophen gouty and non gouty persons respond in a similar manner The faculty of the kidney to maintain urate clearance in gouty patients with a decreasing glomerular activity bespeaks for a superior rather than an inferior ability of the excretory apparatus to handle urate This adjustment continues into the preterminal stages of renal insufficiency Gouty patients with azotemia may have a urate clearance that is essentially normal but a urate reabsorption that is depressed 30 or 40 per cent [7] Urate clearance approaches zero in the terminal stages of renal impairment because of a critical depression in glomerular filtration rate It is concluded that no constitutional inferiority of the kidneys of gouty patients to excrete urate has been demonstrated and that renal changes in patients with gout are the result of gouty and secondary non gouty processes and are not the cause of the metabolic dyscrasia

Increased formation of urate by the body is the third and concluding hypothesis that has been advanced to explain the metabolic disturbance The writer has been partial to this theory because most of the observations collected in his laboratory have supported it indirectly although conclusive evidence has not been forthcoming An augmentation of purine metabolism and a concomitant increase in urate content of body fluids need be very small to account quantitatively for the deposition of urate in most gouty patients Thus the theory may still be valid in the absence of conclusive evidence which shows a striking increase in urate formation Secondly a persistent increase in total daily excretion of urate has been demonstrated in a group of gouty patients[140] Thirdly the increased concentration of serum urate in non affected relatives of gouty patients most likely is caused by an increased formation[151] Finally patients with leukemia a disease known to be associated with an increased metabolism of purine substances may develop gouty arthritis as a complicating malady These data when considered in conjunction with evidence that refutes the first two theories are responsible for our conclusion that the metabolic dyscrasia in gout is most likely one of increased production of urate by the body

Pathogenesis of Symptoms

Symptoms in gouty patients are linked with the deposition of sodium urate in articular structures periarticular structures and in soft tissues The various speculations regarding the mechanism of deposition have been discussed in the section on Morbid Anatomy Urate infiltration of joint structures presumably precedes acute symptoms and once struc

tures have been invaded they are never immune from the likelihood of an acute attack The local pathological mechanism of an acute attack of gouty arthritis is not known Precipitation of urate crystals may or may not be increased during the acute episode The poly articular nature of many of the attacks suggests that a systemic dis turbance rather than a purely local one is responsible

Clinical Description

Acute Gout

Gout rarely produces symptoms prior to the onset of articular dis tress[153] A medical history taken with meticulous care in the pre attack stage may not reveal even a suspicion of gout and the physical ex amination is equally non informative even after several articular at tacks The acute attack of gouty arthritis conventionally is the first sign of the metabolic dyscrasia and the diagnosis usually is not sus pected until after this event The metatarsal phalangeal joint of the great toe is prone to be involved early in the natural history of the malady The acute attack is sudden in onset and may fall on the pa tient like a bolt from the blue [1] It may appear at any time of the 24 hours but is reputed to come in the dead of the night as testified from personal experience by Sydenham[147] The Patient goes to bed and falls asleep in good health but about two hours after Midnight he is awakened by a Pain which usually affects the great Toe The pain becomes progressively more excruciating It has been described as similar to the dislocation of a bone the gnawing of an affected joint by an angry dog the instillation of molten lead or the compression of a joint in a vise The pain is caused in part by an effusion in the joint space and edema of the surrounding soft tissues Tenderness usually is maximal on the lateral aspects of involved joints The attack may be monoarticular or migratory polyarticular An acute gouty joint mimics a septic process and shows the cardinal signs of inflammation Garrod indeed held that if a medical man by chance entirely ig norant of the nature of gout were to see a toe affected by this disease in its full intensity swollen hot red and tender he would probably think that the affection must of necessity terminate in suppuration yet I believe this never happens as the result of simple gouty inflam mation The inflammation extends beyond the joint at times with involvement of the lymphatics similar to a cellulitis[6] Two points of differentiation should be noted lest a surgical consultant deem it neces



Fig 20 Cartilage of terminal phalangeal joint completely eroded by urate deposits Irregular periosteal new bone formation subchondral tophi in metatarsal phalangeal joint of great toe patient No 50 compare with Fig 46

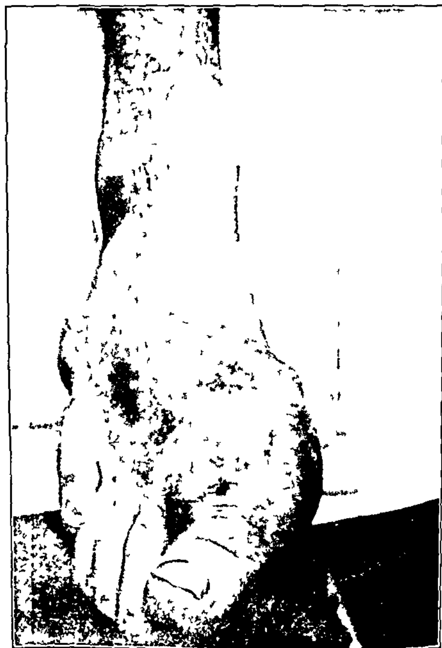


FIG 21 Gouty foot showing extensive urate infiltration in subcutaneous spaces patient No 84



FIG 2 Gouty hands Index finger amputated several years ago because of discharging tophi patient No 84

sary to incise and drain for suspected pus The skin is tense and shiny in a gouty joint and the color tends to be a cyanotic purple rather than a fiery red The writer has observed the coexistence of joint sepsis and acute gouty arthritis only once An acute gouty joint without complications in patient No 49 was suspected of being septic by an uncautious physician Incision was advised and performed but *no purulent material* was obtained Several days later the patient appeared at the *Massachusetts General Hospital* with a streptococcus infection of the tendon sheath Amputation of the finger was necessary In retrospect it seems likely that streptococci were introduced at the first operation or shortly after and that previous to this incident the joint had been sterile

Acute attacks of gout tend to involve only articular structures although non articular tissue may be affected independently of a neighboring joint A subcutaneous tophus or a bursa which has been infiltrated with urate may become acutely involved and be extremely painful The systemic reaction may be indistinguishable from that which accompanies an acute articular episode Headache tachycardia chills malaise anorexia leucocytosis an increase in *sedimentation rate*



Fic 23 Gouty foot Large di charging sinu at lateral aspect of great toe patient No (sagittal sectic n of great toe i shown in Fig 16



Fig 24 Tophi in head of humerus Compare with Fig 31 Periosteal new bone formation along superior margin large soft tissue tophus patient No 74

and a temperature as high as 104° F may be observed The urine output may be scant as with any acute febrile response if abundant quantities of fluid are not taken Large joints notably the knee may be the site of a massive effusion and may require one or more aspirations for the relief of pain Roentgenograms of acute gouty joints are similar to those taken between attacks except for the soft tissue swelling

The duration of an attack depends upon several factors Symptoms may persist for only a few days if the attack is mild One or more weeks may elapse before rehabilitation is apparent following a severe attack Occasionally one encounters a patient with severe joint symptoms which persist for several weeks This may be caused by a repetitive series of single attacks or by one prolonged episode The



Fig 23 Gouty foot Large discharging sinus at lateral aspect of great toe patient No 6 sagittal section of great toe is shown in Fig 16



FIG 24 Tophi in head of humerus Compare with Fig 51 Periosteal new bone formation along superior margin large soft tissue tophus patient No 74

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differentiation is academic since the patient is continually miserable and handicapped by joint distress. Patients with advanced gouty changes and extensive urate deposits usually are the victims of prolonged bouts of articular distress. The above statements apply mainly to untreated bouts. Treatment is the most important single factor in the determination of the duration of the attacks. Adequate treatment may abort a mild one and markedly shorten the duration of a severe one.

The subsidence of an attack is accompanied by diminution of local



FIG 25 Sacro iliac joints normal by x ray. Compare with Fig 26 patient No 74.

inflammation and regression of systemic symptoms. If regional symptoms have persisted for several days desquamation of the involved areas may be the final evidence with but one exception of an acute episode. Restoration of function of an affected joint may be incomplete for some time not that the subject is unable to use the joint normally but full confidence of complete restoration of function may not return for several weeks.

There is a certain constancy among patients regarding the joint involved during the first attack. Scudamore[139] has compiled a large series of observations on this subject. Among 516 cases the great toe of one

foot only was attacked first in 314, approximately 60 per cent. In 27 cases both great toes were involved initially; insteps, ankles, heels, knees and hands, respectively, were affected in the remainder of the group.



FIG. 26. Sacro-iliac joints shown four years later than those illustrated in Fig. [illegible]. Multiple tophi and generalized decalcification; changes are similar to those seen in advanced rheumatoid arthritis or tuberculosis of bone. Patient No. 74.

Premonitory symptoms have been given a great deal of attention, particularly in the writings of the latter part of the 19th century. Stories are recounted of patients complaining of depression, insomnia, bad dreams, nightmares, flatulence, constipation, epigastric distress, anorexia, hemorrhoids, coated tongue, nausea, vomiting, recession of the gums and palpitation. Undoubtedly many persons have a premonition of an impending attack, but many of the symptoms can be attributed *to or are associated with precipitating factors and are not an integral* part of the incipient stages of acute gouty arthritis. This will be discussed in the next section.

The interval between attacks varies considerably. Several years usually elapse and in unusual instances a score of years may separate attacks in the early years after onset of articular symptoms. The interval tends to be shorter as the disease progresses and eventually there

are one or more attacks each year Chronic deforming changes probably have developed at this late stage

Chronic Gout

The boundary line between acute and chronic gout is completely arbitrary nevertheless when the disease has made a great inroad into



Fig 27 Large tophus in olecranon bursa White plaque of urate covers a sinus which discharged periodically x ray of elbow shown in Fig 43 patient No 49

the constitution and its attacks have become frequent the affection assumes a form to which the term Chronic Gout may properly be applied and though it may not cause such excruciating suffering as the more rare and intense visitations of the acute disease still by its protracted duration it is apt to induce a depraved state of the whole system and lead to distortion and rigidity of the joints [5] The development of deforming changes which fortunately are uncommon is usually the result of many acute attacks over a period of years We have never

observed a patient with demonstrable permanent damage following only one acute attack Garrod however affirmed that he had seen ankylosis in a patient who had had but one acute episode

The presence of extensive urate deposits does not necessarily mean that the patient is continually in the throes of an acute attack In fact with adequate treatment acute attacks may be infrequent in comparison to the incidence in patients with less severe changes but who are inadequately treated The irreparable changes are apparent by x ray and physical examination

The majority of the joints of the hands and feet (Figs 20 21 22 23) and arms and legs may be involved Occasionally the shoulder (Fig 24) sacro-iliac (Figs 25 26) or sterno clavicular joints are invaded Marked limitation of motion or ankylosis is the fate of many joints[97,100,104] Urate deposits are widely disseminated in joint spaces joint capsules along tendons and in bursæ (Fig 27) Their appearance in skin has been called gravel of the skin The hands feet (Figs 1 and 2) and knees may be considerably larger than before infiltration with urate One or more sinuses (Fig 27) may communicate with urate deposits and chalky material is aspirated without difficulty A lumbar kyphosis develops and the patient loses stature if vertebral bodies and intervertebral spaces are involved[67] Eventual commitment to bed as a permanent cripple because of chronic gouty changes has happened to only 2 patients in our series

Precipitating Factors

Indiscretion in eating and drinking has been held responsible by many writers for inciting acute attacks some even go so far as to lay the blame for the disease on these agents Gout is an hereditary metabolic malady and is believed to be *relatively immune to incidental items* such as food and drink The presumption that particular foods except those of high purine content are harmful to gouty patients is not an empiric observation it is a prejudice Even high purine foods do not invariably provoke an acute attack and are not reliable as a provocative agent in the diagnosis of the malady

There are several agents which have a much closer relationship to acute gouty arthritis than articles of sustenance These include drugs trauma acute infections and surgical operations Liver extract when given either orally or parenterally has offended some gouty patients[70,41] The pathogenesis may be twofold Liver extract is high in content of purine substances and the increased intake of them alone may be re

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Fig 28 Urate needles as seen microscopically They were removed from a tophus about the great toe (shown in Fig 23) and without chemical treatment or alteration were photographed under a microscope patient No 6

sponsible An alternate theory is related to the hematopoietic action of liver extract Krafka[59] believes that any bone marrow stimulant may incite an attack of gouty arthritis Thiamine hydrochloride which has been recommended in the treatment of gout has been shown to induce an



Fig 9 Moderately advanced gouty changes in metatarsal phalangeal joint of great toe Multiple tophi no destruction of cartilage or narrowing of joint space except in phalangeal joint of fourth toe dorsalis pedis artery shows calcification patient No 54



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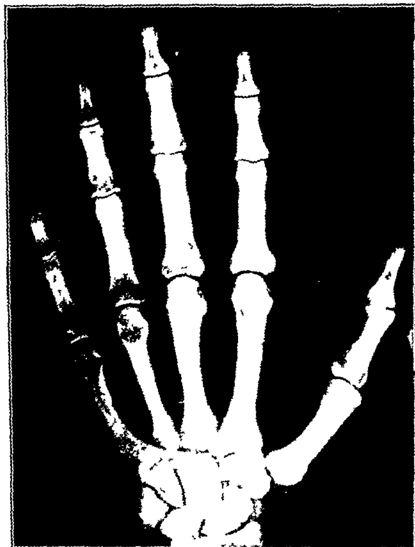


Fig 31 Right hand of patient No 74 x ray taken in 1932 No demonstrable changes by x ray compare with Figs 35 and 36



FIG 30 Right foot of patient No 74 x ray taken in 1932 No demonstrable changes by x ray compare with Fig 37 and 38

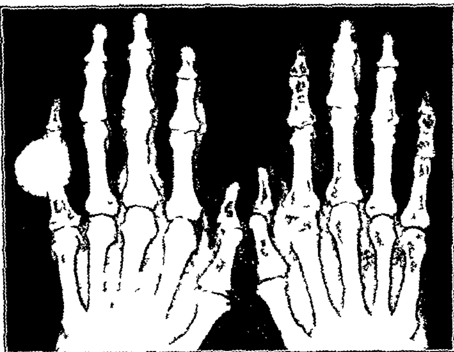


Fig. 33. Multiple osseous and subcutaneous tophi in hands. Pathological fracture of fifth finger within a soft tissue tophus; remainder of joint spaces appear normal; slight generalized decalcification; patient No. 38 (compare with Figs. 32 and 34).

as inciting attacks of gout include exposure to cold and to dampness, extensive blood loss, purgation either medicinal or diarrheic, and foreign protein administration.

Complications

Renal Disease

Kidney impairment is the only serious complication that is encountered in gouty patients. In a series of 77 autopsied cases of gout, Cudzent found only 4 that showed no evidence of kidney disease. Vascular nephritis, interstitial nephritis, gouty kidney and renal impairment in gout have been used to describe the renal perturbation. None of the terms describe adequately the pathological lesion. A slight trace of albumin in the urine and a few formed elements in the centrifuged

attack in a high percentage of cases[161] Salyrgan insulin and ergotamine may do it occasionally The mechanism of inciting an attack by these drugs is not known

Direct trauma offers a readily acceptable explanation A joint already the victim of urate deposition may be incited to inflammation by a blow It is possible that poorly fitted shoes or tight gloves may furnish sufficient trauma to produce symptoms

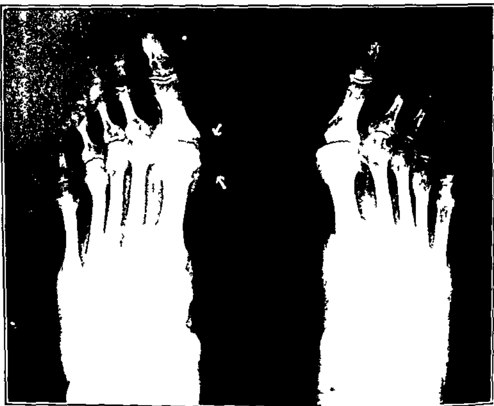


FIG 3 Moderately advanced gouty changes in feet of patient No 64 Osseous and subcutaneous tophi no destruction of cartilage or narrowing of joint spaces

Acute infections are bad associates of gout An acute pharyngitis sinusitis or other types of upper respiratory infections may be complicated a few days later by an acute articular attack[15] Finally surgical operations are potential offenders Duckworth[23] first noted that fits of gout may be brought on by operations In recent years Hench[63] has called particular attention to the diagnostic significance of post-operative gouty arthritis Other factors which have been mentioned

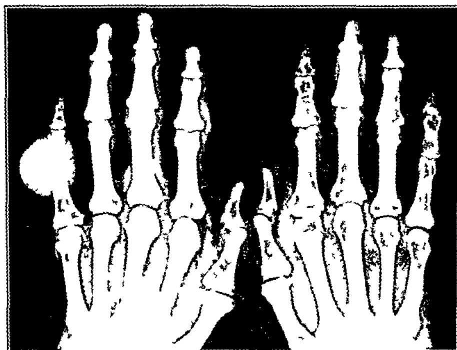


Fig. 33. Multiple osseous and subcutaneous tophi in hand. Pathological fracture of fifth finger within a soft tissue tophus; remainder of joint spaces appear normal; slight generalized decalcification; patient No. 38; compare with Figs. 50 and 54.

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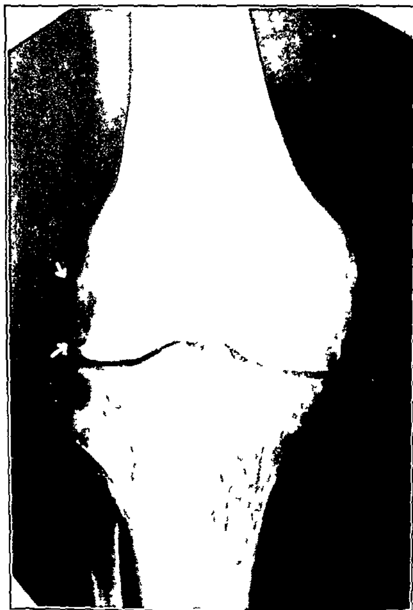


Fig 34 Osseous tophi in knee joint Destruction of cartilage hypertrophic lipping patient No 74

sediment may be noted in the early stages of the dyscrasia[130] A diagnosis of chronic nephritis might be assumed if proper emphasis were not given to the history past or present of joint symptoms The progression of renal damage in gouty patients may be very slow and many

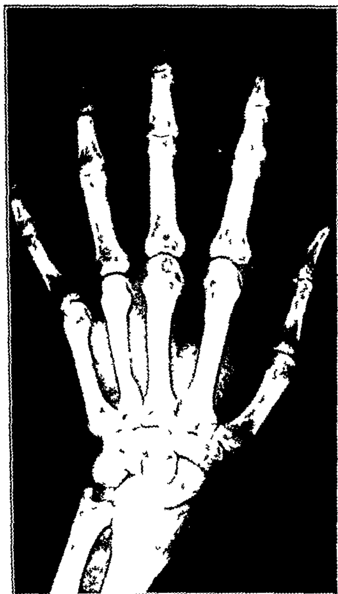


FIG 35 Multiple subcutaneou and osseous tophi x ray taken in 1936 Joint spaces appear normal patient No 74 compare with x ray of same hand hown n Fig 31

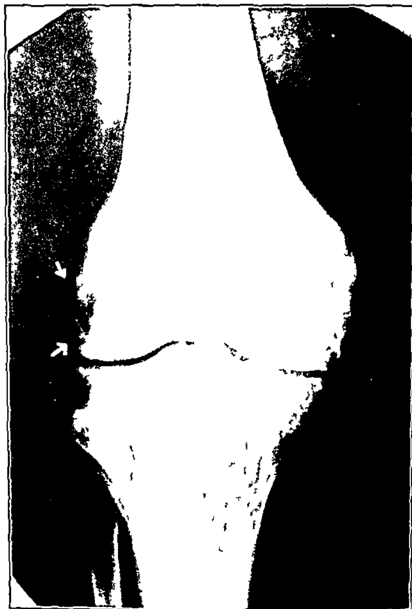


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FIG 37 Mult pl subcutaneous and osseou tophi x ray taken in 193(patient No 74 compare w th ame foot shown n Fig 30

develops finally

Progression of the lesion is low even at this stage and the non protein nitrogen of the serum may be elevated above normal for one or more years before death from uremia closes the case study *Almost all* gouty patients who die before the age of 50[138] and a significant per centage of those in the older age groups succumb because of this renal complication



FIG 36 Further progression of gouty changes shown in Fig 35 as in x ray taken in 1939 Expansion and destruction of cortex of bone destruction of cartilage widespread destruction of tarsal patient No 74

years may elapse before quantitative tests of renal function indicate impairment The inability to concentrate solids delayed excretion of phenolsulphonphthalein dye and poor concentration of a radio opaque dye during pyelography follow in approximately this order Azotemia



FIG 37 Multiple subcutaneous and osseous tophi x ray taken in 1936 patient No 4 compare with same foot shown in Fig 30

develops finally

Progression of the lesion is slow even at this stage and the non protein nitrogen of the serum may be elevated above normal for one or more years before death from uremia closes the case study Almost all gouty patients who die before the age of 50[139] and a significant percentage of those in the older age groups succumb because of this renal complication



FIG 38 Further progression of gouty changes shown in Fig 37 x ray taken in 1939 patient No 74

The observations on renal function that we have collected have been tabulated from two series of patients The data on a representative group of 26 patients of various ages have been given in Table VII The patients were selected without regard to the severity of the disease

or to the duration of symptoms Each patient that was seen during the period of study either in the out patient clinic or in the hospital is included Several were admitted to the hospital for investigation at our request and did not require hospitalization because of the severity of the disease They are believed therefore to be representative and not exclusively a group of severely afflicted patients Routine clinical tests for renal function as well as precise tests such as glomerular filtration rate renal blood flow and maximum capacity of the tubules

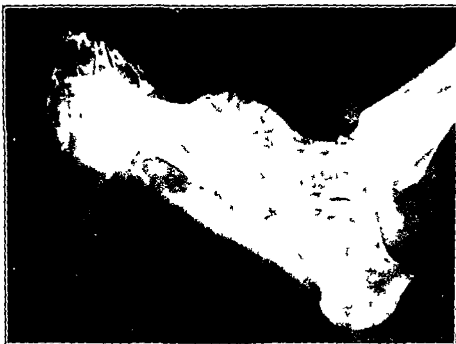


Fig 39 Lateral view of foot shown in Fig 38 patient No 74

for excreting diodrast were performed In portion of the table shows that less than 25 per cent had retained the ability to concentrate solids maximally or had a glomerular filtration rate above 100 c c per minute A group of 50 patients fifty years or older is included in the second series which has been published elsewhere[155] Again no attempt at selection was made The criteria for inclusion in this group were the diagnosis of gout and the age of the patient Routine clinical tests only were performed and the precise tests were omitted There is some overlapping of patients in the two series Approximately 50 per cent



FIG 40 Destruction of cartilage and narrowing of phalangeal joint space by urate deposits Hypertrophic change about both joints of great toe patient No 60

showed an impairment of one or more functions of renal excretion It is believed that if additional tests had been performed the results would have shown a similar high percentage of pathological kidneys as in the first series The conclusion seems inescapable that the majority of patients with gout irrespective of age or duration of symptoms have impairment of renal function

The pathogenesis of the renal lesion in gout in the first years after onset of symptoms is not known. A logical sequence of events may be postulated according to the writer's theory of the etiology of the morbid disturbance. An increased formation of urate by the body leads to an



FIG 41 Huge subcutaneous tophi about great toe. Erosion of metatarsal phalangeal joint. Joint space appear normal. patient No 37

increased content in the body fluids and an increased amount available for excretion in the urine. The latter process continues until renal impairment becomes clinically apparent. The solubility of urate in glomerular filtrate approaches the maximum and precipitation of sodium urate occurs during the concentration of urinary solids in the tubules. This process leads to some damage in almost all patients and serious damage in many. Urate crystals may remain in the tubules, may be passed into the renal pelves and act as a nucleus for urate calculi, or the crystals may be carried down the ureters and eventually be voided. The presence of urate crystals in the tubules is not a normal situation



Fig 42 Extensive osseous and subcutaneous tophi in knee x ray taken in 1939 Hypertrophic changes no ankylosis patient No 74



FIG 43 Larg olecranon tophu No erosion of cortex large spur at insertion of triceps tend n hypertrophic changes about glenoid fos a pat ent No 49 same elbow a h wn in F g 27



Fig 42 Extensive osseous and subcutaneous tophi in knee x ray taken in 1939 Hypertrophic changes no ankylosis patient No 74

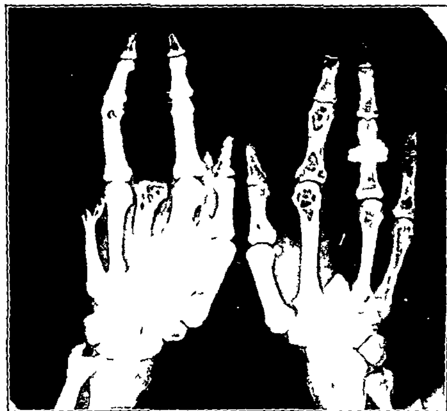


Fig 47 Diagno i Boeck s sarco d Multiple area of d m ni hed len ity marked thinning of phalanges joint appear normal no clinical e idence rf gout cr mpare w th Fig 36

found it necessary to remove urate calculi by surgical manipulation ince the stones are relatively friable and will be expelled by conservative treatment

Hypertension and Arteriosclerosis

The incidence of these conditions (Fig 29) i higher in young gouty patients than in young patients suffering from other types of chronic diseases [75, 79, 80] Their incidence is significant but le s noteworthy in gouty patients in the declining decades of life The a sociation of hyper tension and va cular sclerosis with a reduction in kidney function is a



FIG 46 Diagnosis hypertrophic arthritis and hallux valgus Several areas of diminished density suggestive of osseous tophi no clinical evidence of gout compare with Fig 29



FIG 49 D agnosi syphil of prox mal phalanx of great t e Exten ve erosion and patl ological fracture no cl n cal evidence of go it Wa sermann reaction was positi e marked clin cal response t ant yph l tic treatm nt compare w th Fig 33



FIG 48 Diagnosis Boeck's sarcoid Feet of patient shown in Fig 47 compare with Fig 37

frequent clinical observation The precise tests of renal function show an increase in filtration fraction in patients with malignant hypertension and renal impairment No such increase in filtration fraction is noted in gouty patients One might argue from this finding that hypertension and renal disturbance in gout have not as intimate an association as is presumed to exist in malignant hypertension Clinical observations confirm this In our series of patients no instance of malignant hypertension was seen the hypertension which was noted corresponded more closely to the benign type It is believed that the pathogenesis of hypertension and premature vascular sclerosis in gouty patients remains obscure



FIG 49 Diagnosis syphilis of proximal phalanx of great toe Extensive erosion and pathological fracture no clinical evidence of gout Wassermann reaction was positive marked clinical response to antisyphilitic treatment compare with Fig 33

Muscle Atrophy

Muscle wasting is caused by loss of tone and diminution of function of affected joints and is not a specific consequence of acute or chronic gouty arthritis A minimal amount of atrophy appears during and

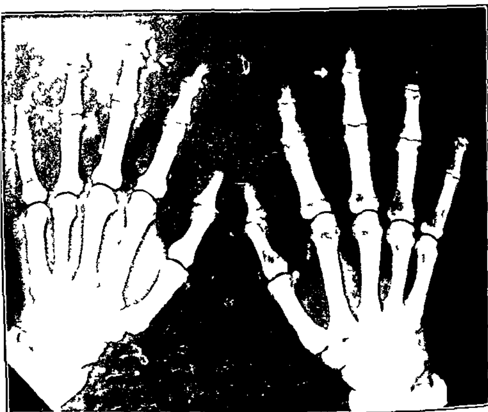


Fig 50 Diagnosis multiple gangliomata and hypertrophic arthritis Multiple areas of diminished density no clinical evidence of gout compare with Fig 36

after an acute paroxysm but rarely is it of clinical significance Patients with ankylosed joints and advanced gouty changes may have a severe grade of muscle atrophy

Miscellaneous Complications

It has become common to ascribe bronchitis dyspepsia gastralgia iritis gravel cystitis and even psoriasis to the gouty diathesis but the evidence is very slight and the gout to which such evidence as

there is applies is the distillation of morbid humours which belongs to a bygone pathology."[9] We can subscribe in large part to this acrimonious remark and would lengthen the list by the inclusion of phlebitis, glycosuria, pharyngitis, *migraine and neuritis*. We are reluctant to call any complication gouty unless it is associated with deposition of urate



FIG. 51. Diagnosis: multiple myeloma. Multiple areas of diminished density; no clinical evidence of gout. Compare with Fig. 74.

or has an unusually high incidence in gouty patients. Instances have been reported of gouty patients coughing up urate broncholiths[5]. A *diagnosis of gouty bronchitis possibly* is permissible under such circumstances. Weve[166] has described deposition of urate crystals in the lens of gouty patients. Dr. F. Gunderson examined the lens of approximately 30 patients with a slit lamp in our series in the pursuit of this phenomenon. Evidence of urate crystals was not observed in any. The matter of skin lesions was investigated by us in a slightly greater number. Less than 10 per cent had evidence of either psoriasis or

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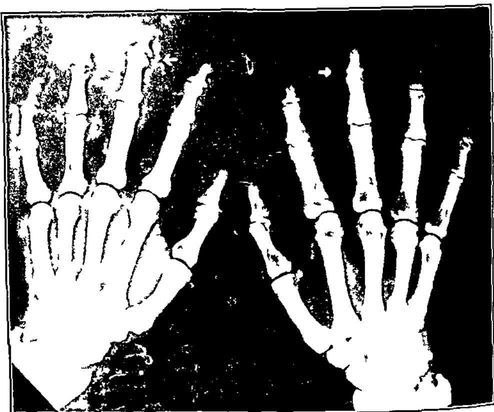


Fig 50 Diagnosis multiple gangliomata and hypertrophic arthritis Multiple areas of diminished density no clinical evidence of gout compare with Fig 56

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all three are considered to be metabolic dysfunctions and have a high familial incidence. Talbott[33] observed 4 patients with diabetes mellitus and 3 with glycosuria in a series of 194 gouty patients. Obesity was present in 47. The percentage of diabetics with a tendency to gout has been recorded as high as 8 per cent.[56] Joslin's[41] statement of a much smaller percentage is representative of the incidence in the United

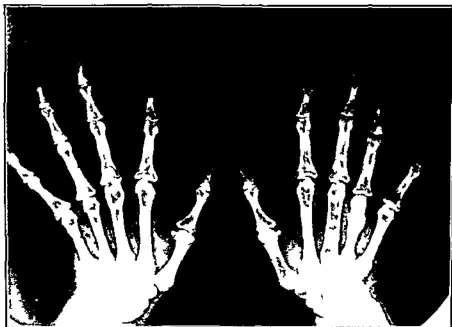


FIG. 53. Diagnosis: hyperparathyroidism. Multiple areas of diminished density, erosion of terminal phalanges, generalized decalcification, expansion of bony structures and thinning of cortex, pathological fracture of fourth metatarsal of right hand; no clinical evidence of gout (compare with Fig. 33).

States. Less than three per cent of the total patients with gout that we have seen have had diabetes mellitus. The diabetes as well as the gout has been mild in these patients. We have not been impressed with the obeseness of our gouty patients. Some are overweight; the majority are not. Obesity should be corrected if present, but it probably is not a predisposing factor to gout.

Leukemia and gout occasionally coexist. The increased purine metabolism of leukemia may well aggravate a mild gouty affliction. Ebstein has reported the excretion of more than 5 grams of urate in 24 hours

eczema Those who had either of these conditions however reported an exacerbation *of local skin symptoms before or during an acute attack* of arthritis

Associated Diseases

There are several clinical entities that have been thought to have a



Fig 5 Diagnosis enchondromatosis Multiple areas of diminished density egg shell appearance of several phalanges no clinical evidence of gout compare *with* Fig 36

particular affinity for gout Lead intoxication diabetes mellitus[16] obesity leukemia[6, 87] polycythemia vera pernicious anemia[81] hemolytic jaundice purpura hemophilia[6, 116] and Paget s disease have been so suspected Garrod was one of the first to comment on the association of lead poisoning and gout This matter has been treated in the section on Etiology *It was concluded that lead intoxication* and gout rarely occur together in the United States Diabetes mellitus and obesity occupy a similar position in our experience Grafe[4] however believes that they may have a close constitutional *relationship* to gout since



FIG 55 Diagnosis traumatic arthritis hallux valgus Multiple areas of diminished density in head of first metatarsal no destruction of cartilage no evidence of fusion compare with Fig 9

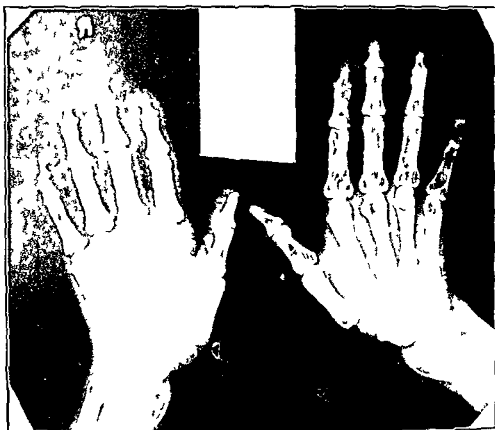


FIG 54 Diagnosis Paget's disease of bone generalized Multiple areas of diminished density generalized decalcification and wide trabeculation no clinical evidence of gout compare with Fig 35

in a patient with both maladies We have seen only one patient with gout and leukemia Polycythemia vera may be complicated by leukemia and it is conceivable that this phenomenon in a gouty patient is responsible for the supposed association of polycythemia vera and gout Purpura hemophilia[3] and chronic erythronoclastic anemia[91] have been reported in gouty patients

Patients with pernicious anemia formerly were given considerable quantities of purines orally or parenterally during treatment with crude preparations of liver Acute attacks of gouty arthritis have followed this therapy Localized Paget's disease of bone has been reported in patients with gout[117 131] There are 2 such instances (patients Nos 42 and 68) in our series Duckworth[3] reported one patient with generalized Paget's disease and gout



FIG 55 Diagno·is traumatic arthritis hallux valgus Multiple areas of d min hed dens ty in head of fr t metatarsal no destruction of cartilage no evidence of fus on compare w th Fig 9



FIG 56 Diagnosis generalized calcinosis secondary to chronic nephritis calcium gout X ray appearance has little to suggest gout but gross appearance was highly suggestive of generalized urate deposits

Diagnosis

Gout is a distinct clinical entity and should be differentiated clearly from the other arthritides. It is most likely that many cases of non-gouty joint diseases were mislabelled gouty rheumatism in ancient and medieval times. This error should be committed on a large scale no longer. Confronted then with a suspected case of gout, whether acute or chronic, what shall be our way of approach? Not the easy and hazardous path of lightning diagnosis affected by those who plume themselves on their so-called clinical instinct, but the slow, laborious route of clinical observation that leads more surely to the vantage ground of the truth; this assuredly in all diseases, but in none more so than in joint disorders whose outward resemblances so oft hark back to inward disparities.[98]

The criteria for diagnosis are numerous and reliable. Difficulty is encountered usually in the earlier stages of the disease before the development of tophi. Gout may be suspected even before the first attack of joint distress if heed is given to two clues. It can not be expected that they will be disclosed very frequently. (1) A positive family history for gout should suggest the possibility of an increased concentration of serum urate in a non-arthritic relative. In the studies of non-affected relatives of gouty patients discussed under Heredity the family history was the only leading evidence[15]. Nevertheless more than a score of subjects were discovered with an increased concentration of serum urate. (2) The second clue is the passage in the urine of a urate calculus. Although many patients who pass urate calculi are not suffering from gout and do not develop gouty arthritis subsequently,[150] it may be expedient to determine the concentration of serum urate whenever a urate calculus is passed.

The diagnosis of gout after the development of joint distress and before the appearance of tophi should be founded upon all or the majority of the following data: (1) family history of gouty arthritis, (2) one or more acute attacks of joint pain, (3) increased concentration of serum urate, (4) therapeutic response to full doses of colchicine, and (5) evidence of renal disturbance.

A *family history* of gout may suggest the diagnosis which would not otherwise be considered at the initial consultation. As many generations as possible should be included in the genealogical study, since gout may skip one or more generations.

Recurring attacks of acute joint pain with completely asymptomatic intervals are seen infrequently except in gout. The sudden onset of

pain, rapid appearance of signs of inflammation and monoarticular or polyarticular involvement in an otherwise healthy person are highly suggestive.

The *concentration of serum urate* is elevated in gouty patients irrespective of the presence of acute or chronic symptoms. This diagnostic procedure is particularly significant in patients under consideration who have not developed subcutaneous or intraosseous tophi. Either the method described by Benedict and Behre[5] or that described by Folin[4] may be employed for the colorimetric estimation of urate in serum. Certain modifications of the procedures as originally described by them are expedient. The determination should be done on serum or plasma rather than on whole blood. Serum or plasma is to be preferred to whole blood for the determination of most constituents. Since many of the chemical constituents of the blood are distributed unequally between the serum and cells, any fluctuation in cell volume will affect the final result on whole blood even though no change in concentration of the constituents in either cell or serum phase has occurred. Avoidance of intracellular substances which interfere with the color development in the urate procedure is an additional argument in favor of the use of serum and against the use of whole blood. The final readings are to be made, if possible, in a photocolorimeter[36] in preference to a DuBoscq colorimeter. The range of uric acid concentrations in serum or plasma is somewhat above that reported for whole blood. The upper range for normals in whole blood is approximately 4.0 mgm. per 100 c.c.[41, 83, 14] and that for serum or plasma is approximately 1 mgm. higher. Experience has shown that most non-gouty persons have a serum urate less than 5.0 mgm. and most gouty patients have a level greater than 6.0 mgm. There is a supplementary advantage, therefore, in using serum because of an intervening range of 1.0 mgm. between 5.0 and 6.0 mgm. which separates most non-gouty individuals from gouty patients.

Conditions other than gout which may be associated with an elevated uric acid content of the serum include renal insufficiency, leukemia, polycythemia vera[35, 71], pernicious anemia[53], lead poisoning[17], starvation[93] and certain acute infections such as pneumonia. The elevation of serum urate in most of these maladies is of academic interest except when the association with gout is a possibility. The elevation of serum urate in renal insufficiency, however, is of more than academic concern. Since renal insufficiency, to be sure mild in many instances, frequently develops in patients with gout, one must be cautious in interpreting the urate level in any patient with joint disease and renal

impairment. This is particularly applicable to patients past the age of 50 who develop mild renal insufficiency as an integral part of senescence.

Response to colchicine of an acute gouty joint usually is convincing and the diagnostic implications are significant. Full therapeutic doses of colchicine should be given as discussed under Treatment. Inadequate amounts of colchicine provide little symptomatic relief and may give, therefore, a misleading diagnostic answer. Non-gouty types of arthritis do not respond to colchicine.

Renal disturbance may be apparent at the time of onset of joint symptoms in some patients. It will be delayed for several years in most others. Few enjoy immunity from renal dysfunction throughout the natural course of the disease. The high incidence of renal disease is not observed in any other type of acute or chronic arthritis except arthritis associated with disseminated lupus. Diagnostic confusion of gout and lupus is not anticipated because of the many distinguishing features of both maladies.

Years after the onset of acute arthritic attacks, the classic pathological stigmata of gout are evident. These are urate tophi and roentgenological changes; for completion these should be added to the five diagnostic data enumerated earlier in this section on diagnosis.

Urate tophi appear in periarticular structures and on certain cartilages not related to joints. One or more white nodules on the helix of the ear are telltale signs of gout. Subcutaneous tophi elsewhere on the body may be more difficult to identify on physical examination. Recovery of a portion of the contents for chemical identification is to be recommended strongly. The chalky contents may be obtained very easily if the subcutaneous tophus has developed a sinus. All suspected tophi that are removed surgically, either for biopsy or for other purposes, should be examined carefully. A portion should be sent to the pathological laboratory for proper fixation (see Morbid Anatomy) and microscopic examination of a prepared section. The remainder of the contents should be studied without further preparation as discussed below. A small quantity of the contents of tophi that are not removed surgically may be aspirated with a hypodermic needle and syringe. Whichever method is employed to recover material from a tophus, the contents are identified by one or more of the three following procedures: (1) the murexide test, (2) the colorimetric test, and (3) the crystallographic identification.

The murexide test is not difficult to perform.[103] A small portion of the suspected urate sludge is heated in a porcelain dish with a few drops of dilute nitric acid. A reddish colored residue, alloxan, remains when

all of the nitric acid is driven off A few drops of ammonia solution are added after the dish is cool and a purplish red color develops due to the formation of murexide or purpurate of ammonia The interpretation of this procedure may be more difficult than the others A qualitative colorimetric test for uric acid may be done on the aqueous solution of a small amount of contents of a tophus Either the Benedict or Folin reagents may be used

The crystallographic identification is simple and reliable The contents of a tophus are placed upon a microscopic slide covered with a glass slip and without additional treatment are examined under low power magnification of a microscope The needle like crystals should be abundant if sodium urate is present (Fig 28)

Roentgenological evidence of changes (see Figs 12–15 20 25 26 and 29–56 on previous pages) in the bones of the extremities of gouty patients were demonstrated first by Huber in 1896[6] Several of the findings which he stressed as characteristic of gout, are caused by deposits of sodium urate in cartilage or in bone Calcium salts are replaced by sodium urate in the formation of tophi in bone and increased radiability of the involved areas results Tophi must attain a considerable size perhaps 5 mm or greater in diameter before they are visible by x ray (Fig 29) and their identity reasonably assured

Very few normal joints from gouty patients are illustrated in this review Most of the joints show moderate or advanced changes The proportion of pathological joints illustrated therefore gives an exaggerated index of the incidence seen in the out patient department and hospital In the first years after the onset of acute attacks the x ray examination usually is negative (Figs 30 31) save for soft tissue swelling during an acute episode The presence of demonstrable tophi in bone is indicative of irreparable joint involvement and is evidence that the joint has been the site of several acute exacerbations The metatarsal phalangeal joint of the great toe is one of the first structures to show chronic changes by x ray (Fig 32) Other joints of the feet hands (Fig 33) and knees (Fig 34) show involvement subsequently Tophi usually are multiple further proof of the polyarticular nature of the disease The joints show progressive damage as the disease advances Figures 30 31, 35 36 37 38 and 39 illustrate this statement The pictures show progressive urate deposition over a 7 year period in the hands and feet of patient No 74 Figures 30 and 31 show no pathological changes Many of the bones in Figures 36 and 38 have the appearance of egg shells or Swiss cheese and show as advanced changes as we have seen in any gouty patient Figure 40 is presented for con

trast The phalangeal joint of the great toe shows extensive destruction and ankylosis of the joint space with minimal destruction of the epiphysis

Soft tissue swelling about the joint is apparent at the first only during the acute attack but this becomes permanent (Fig 41 42) with the development of subcutaneous tophi Tophi may develop in a tendon a bursa or other structures immediately adjacent to bone without demonstrable damage to the contiguous periosteum (Fig 43) Subchondral tophi which invade the epiphysis and at times the diaphysis of the bone do not break through the periosteum except immediately adjacent to the joint Local disturbances of calcium metabolism may be deduced from one of several changes noted by x ray Generalized decalcification of the bones of the skeleton is uncommon except in patients who are confined permanently or periodically to bed

The diagnosis of gouty arthritis from the finding of an area of increased radiability is as unreliable as is the exclusion of the diagnosis merely because the x ray examination is negative There are several conditions which have certain similarities to gout by x ray Examples of rheumatoid arthritis (Fig 44) psoriatic arthritis (Fig 45) chronic trauma (Fig 46) Boeck s sarcoid (Fig 47 48) syphilis of bone (Fig 49) multiple ganglionata (Fig 50) multiple myeloma (Fig 51), enchondromatosis (Fig 52) hyperparathyroidism (Fig 53) Paget s disease (Fig 54) hallux valgus (Fig 55) and generalized calcinosis (kalkgicht)[176] (Fig 56) are illustrated The diagnosis of gout was considered by the roentgenologist in several of these instances although the differential clinical diagnosis usually did not include gouty arthritis

Differential Diagnosis

The several arthritides offer the chief difficulties in the clinical differentiation of gouty and non gouty disturbances In addition an acute gouty joint may be confused with cellulitis

Acute rheumatic fever with joint involvement polyarticular rheumatism may simulate gout polyarthritis uratica particularly in young persons The arthritis may be monoarticular or migratory polyarticular in either disease Elevation of temperature leucocytosis increased sedimentation rate soft tissue swelling by x ray and an exacerbation following a surgical operation are not distinguishing features during the period of acute symptoms An upper respiratory infection may precede either type of arthritis Acute rheumatic fever has a predilection for large joints while gout prefers the smaller ones Arthralgia in rheumatic

all of the nitric acid is driven off A few drops of ammonia solution are added after the dish is cool and a purplish red color develops due to the formation of murexide or purpurate of ammonia The interpretation of this procedure may be more difficult than the others A qualitative colorimetric test for uric acid may be done on the aqueous solution of a small amount of contents of a tophus Either the Benedict or Folin reagents may be used

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of several decades others show rapid and precarious progression in only one or two decades It is believed that while the disease progresses in all patients after the first turbulent episode the rate of progression is the unknown component A good index is the frequency and duration of acute attacks Patients who have several attacks *per year* and who untreated might spend a total of several weeks in bed show a more rapid progression of structural changes than patients who have not more than one or two attacks per year The younger the person afflicted the greater the anatomical involvement[101] The two patients in our series who are obligatory cripples and confined to bed a greater part of the time are 34 and 45 years of age respectively We have not seen any patient who had the first attack of acute arthritis after the age of 50 develop any serious polyarticular pathological lesions

Even less definitive data are available regarding the prognosis of renal impairment This is unfortunate since the severity of the renal changes is of greater prognostic significance than the articular changes We have discovered no clues that give any help in predicting the rate of progression of renal lesions Some patients have little or no renal impairment with severe gouty arthritis others show the reverse process Less than 10 *per cent* of the patients in our series have had advanced gouty changes and serious renal impairment Of course such a combination is terminated within a few years by azotemia and uremia A patient may live for many years with advanced joint disease but only a relatively short time with advanced renal impairment Gudzent asserted that prognosis in gout depends solely upon the state of the renal vessels

PREVENTION

The prevention of gout is a problem similar to the prevention of diabetes mellitus i e a eugenic one The disease will never exterminate itself since it is not lethal until after child bearing years Furthermore if it were possible to sterilize all afflicted persons this would not wipe out the disease for several generations

The attempted eradication of an hereditary malady through social hygienic measures that are allowed under existing laws will have only a trifling effect It is thought that the most that can be accomplished at present is enlightenment regarding the possibility of transmitting the disease to children of parents who are afflicted or of individuals who have a family history of gout

fever usually is evoked by motion but in gout it is spontaneous Non articular symptoms such as epistaxis weight loss precordial pain an increase of the P–R interval by electrocardiogram and ultimate development of heart disease point to rheumatic fever Elevation of serum urate and a favorable response to colchicine point to gout

Rheumatoid arthritis has a higher incidence among females than males gout has the reverse sex ratio Both conditions are observed in the middle decades of life Constitutional symptoms such as malaise, weight loss and vasomotor changes usually are seen in rheumatoid arthritis The arthritis is more symmetrical the duration of single attacks is much longer, and the onset is more insidious than that in gout A clinical response to colchicine is trivial Physical examination and x ray changes (Fig 44) show little similarity to gout in the established case of rheumatoid arthritis[6,67] Rarely is the uric acid in the serum elevated

Degenerative joint disease may be confused with gout in patients over 50 Acute articular episodes are uncommon in patients with degenerative joint disease Females are more often afflicted than males while the converse is true of gouty arthritis An acute Heberden s node has a certain similarity to a small gouty tophus a chronic node should not be mistaken for a tophus

Gonorrheal arthritis may be accompanied by articular attacks that are as acute as are encountered in gout The chronicity of gonorrheal arthritis without treatment is a distinguishing feature A history of a genitourinary infection should be obtained in the gonorrheal patient The gonorrheal arthritis may be monoarticular or polyarticular and usually involves the larger joints of the body Gouty arthritis does not respond to the administration of sulfonamides as does gonorrheal arthritis

Acute cellulitis of the hands or feet may be confused with gouty arthritis An acute gouty joint may be incised and drained because of an incorrect diagnosis The development of cellulitis in the vicinity of a joint without the evidence of a systemic reaction to a septic process particularly in a patient with a history of joint disease presents a difficult diagnostic problem The content of uric acid in the serum should be determined if possible before an operation is considered This usually will confirm or disprove a diagnosis of acute gouty arthritis

PROGNOSIS

The severity of the irreparable articular damage varies greatly in a group of patients Some persons are only mildly affected over a period

increased sweating, a diuresis of water and salt and a decreased intake of the same because of loss of appetite. The results of these disturbances lead to dehydration of the body and reduction in output of urine. This in turn leads to an unusually high concentration of urate in the renal tubules. Precipitation of a portion of the urate[57] and subsequent damage to the kidney from this sequence of events may be one of the serious sequelæ of an acute gouty attack. On the other hand, if the fluid intake is abundant, the internal environment of the body is maintained and the volume of urine excreted is upheld. This may be achieved best by broths, soups, fruit juices and milk, fluids which contain minerals as well as calories. Tea, coffee and sweetened beverages are less desirable.

A soft diet with a high percentage of carbohydrates is recommended as for other types of febrile disturbances. No restriction should be placed upon the use of sedatives. Acetylsalicylic acid may be prescribed in amounts up to gr. 100 (6.6 gm.) daily. It is a satisfactory analgesic and in addition is one of the few drugs which promotes excretion of uric acid. Codein, gr. ½ to 1 (30 to 60 mgm.) may be repeated one or more times during the acute attack. Morphine is required infrequently but need not be withheld if the pain is severe and not controlled by other means.

The administration of colchicine is most important. The virtues of the meadow saffron (colchicum autumnale) in gout have been extolled, decried, extolled again and again distrusted and almost denied. Like every other remedy which has done good service in the war against disease it has had to endure the wear and tear of excessive adulation and unreasonable detraction. There can be no question that it has great value or it could not have survived the ordeal.[7] The drug acquired the name colchicum from the old Greeks because the plant grew in Colchis in Asia Minor. It is important in the treatment to distinguish between colchicine and the wine or tincture of colchicum. Various proprietary preparations which have contained colchicum include eau medicinale, Wilson's tincture, Reynold's specific and Laville's tincture.

Colchicine is to be preferred to the wine or tincture of colchicum and to proprietary preparations just mentioned since the colchicum preparations vary in their potency and are unreliable in their action. Crystalline colchicine is of constant potency. It is reputed to have been introduced into the United States by Benjamin Franklin, a sufferer from gout.[137] The standard preparation is the tablet or granule (tabellae colchicinae U.S.P.) which contains gr. 1/120 (0.5 mgm.) of active material. Colchicine has the following structural formula:[55]

Treatment

Sydenham expressed the pertinent presumption that gout is incurable. There are numerous statements to the contrary in the literature however and if one is credulous a more optimistic attitude develops. Drugs, diets and mineral waters have been accredited with curing or at least arresting the malady. We concur in the more pessimistic predication and believe that once the diagnosis is established the patient will have the disease throughout life. This does not necessarily mean that the patient will be afflicted repeatedly with severe attacks. It is known that an asymptomatic period may persist for years, even a decade or two, but eventually attacks will recur. "The absence of typical attacks is not proof that the gouty process as such is cured."[3] No patient is free of the affliction at any time after the first attack if an increased concentration of serum urate ultimately proves to be an integral part of the gouty dyscrasia. There is no sovereign remedy in the sense that it permanently restores the abnormal concentration of urate or leads to regression of bulbous tophi. The most important single factor which determines the length of asymptomatic periods is the severity of the disease rather than any specific treatment. There is, however, much to be gained from the relief of articular symptoms. This will be discussed under acute attacks, interparoxysmal periods and chronic deforming gout.

Treatment of Acute Attacks

The symptomatic response of acute gouty arthritis is most dramatic. This is achieved by the use of colchicine supplemented by certain general measures. Bed rest, an abundant intake of fluids, a soft diet and sedatives are indicated. The joint should be put at rest as early as possible after the onset of acute symptoms and function should be resumed after the attack without undue delay. This latter recommendation is quite different from that approved for other forms of arthritis. A cradle for the bed clothes relieves local pressure upon affected structures. There is no contraindication to the local application of hot or cold compresses although they contribute little. Their soothing action is not great, alleviation of acute symptoms is not striking and the duration of the acute attack is not shortened.

An abundant intake of fluids is important and serves a dual purpose. It combats dehydration and allays precipitation of urate in the kidneys. During an acute attack there is elevation of body temperature

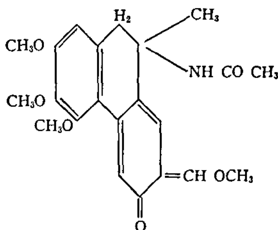
cient in a severe attack to take half of the anticipated dose one day wait 12 hours and complete the dose the following day Once treatment has been started it should be continued without interruption until an adequate amount has been taken If articular symptoms develop in the evening or during the night ingestion should be uninterrupted as during the day It is more important in the treatment of the acute attack that the patient receive colchicine regularly than that he receive a continuous night s rest A sedative such as a barbiturate may be given which will enable the patient to return to sleep after each dose of colchicine if the pain is not too severe

Failure to appreciate the proper method for administering colchicine has been partially responsible for its unenthusiastic recommendation by some physicians and use by their patients The necessity of producing gastrointestinal distress has contributed to its unpopularity Gastrointestinal disturbance is inconvenient but in our experience it does not constitute a contraindication A preliminary carthartic or a purgative is not recommended since it may be impossible to determine whether purgation has followed such a drug or is the indication for cessation of colchicine ingestion

Subsidence of joint pain usually begins after 12 hours and should be complete within a period of from 24 to 48 hours if a sufficient quantity of colchicine has been taken A few attacks less than 5 per cent in our experience are not benefited materially by a single course of colchicine If this be the case a second course should be repeated after a lapse of 2 or 3 days It is unwise to repeat the colchicine earlier since untoward symptoms may develop before an amount of colchicine has been consumed adequate to affect joint symptoms There is little merit in combining colchicine with small doses of salicylate If a salicylate is given from 50 to 100 grains (3 3 to 6 6 gm) daily should be given The ingestion should stop just short of development of symptoms of salicylism

Treatment of Intercritical Periods

Acute attacks of gout in most patients should consume not more than a few days of each year The greater portion of the time then is intercritical or interparoxysmal Attention should be paid during this period to exercise recognition of prodromata intake of foods and fluids and administration of drugs Exercise particularly of affected joints is to be encouraged We have not observed any harm to result from the general application of this recommendation Sydenham be



The pharmacological action of colchicine in gouty patients is not known In 1854 Gairdner[47] maintained that the beneficial action was not related to an increased excretion of urinary urate Recent studies in our laboratory have confirmed this[7] Colchicine has gained considerable fame in recent years because of its action upon mitosis in plants[11] In order to produce this effect it is necessary to give per unit mass of experimental material approximately 100 times the therapeutic dose recommended for gouty patients Suffice it to say we do not need to concern ourselves about inducing cancer by the oral use of colchicine in therapeutic amounts since the gastrointestinal tract rebels if this limit is exceeded by even a few tablets Nor have we observed the development of cancer or any malignant tumor that could be attributed to colchicine in patients receiving therapeutic quantities of the drug daily over a period of several years

Ingestion of colchicine should be started at the first appearance of acute articular symptoms One tablet or granule gr $\frac{1}{120}$ (0 5 mgm) should be taken every 60 or 90 minutes A severe attack may require from 8 to 16 tablets the average is approximately 10 Therapeutic adequacy is determined in the inexperienced patient by the appearance of gastrointestinal symptoms such as nausea diarrhea and vomiting Many patients learn from experience the optimum number of tablets to ingest with each attack of acute gout and are able to obtain the desired alleviation of joint pain without having to submit to excessive gastrointestinal distress Until patients have acquired this information it is imperative that the ingestion of colchicine be carried to the point of development of untoward symptoms before advising cessation[60] The importance of continuous ingestion merits emphasis[154] It is not suffi

cient in a severe attack to take half of the anticipated dose one day wait 12 hours and complete the dose the following day. Once treatment has been started it should be continued without interruption until an adequate amount has been taken. If articular symptoms develop in the evening or during the night ingestion should be uninterrupted as during the day. It is more important in the treatment of the acute attack that the patient receive colchicine regularly than that he receive a continuous night's rest. A sedative such as a barbiturate may be given which will enable the patient to return to sleep after each dose of colchicine if the pain is not too severe.

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Treatment of Intercritical Periods

Acute attacks of gout in most patients should consume not more than a few days of each year. The greater portion of the time then is intercritical or interparoxysmal. Attention should be paid during this period to exercise, recognition of prodromata, intake of foods and fluids and administration of drugs. Exercise, particularly of affected joints, is to be encouraged. We have not observed any harm to result from the general application of this recommendation. Sydenham be-

lieved that exercise had certain preventive properties 'Now these (formation of tophi) may be guarded against whereby we obtain the due diffusion over the whole body of the humours that generate gout instead of their accumulation in any particular part of it by preference I have found in my own person that long and daily exercise not only stops the generation of chalkstone but even dissolves old and hard ones already formed provided only that they have not gone so far as to have converted the outer skin into their own proper substances

Some patients are acutely aware of the prodromata of an impending attack which include polyuria gastrointestinal unrest suppression of sweating and gain in body weight A fall in barometric pressure may accompany some or all of these symptoms[113] just as a decrease in barometric pressure precedes an exacerbation of symptoms in patients with rheumatoid arthritis At the first perception of prodromata and before the appearance of joint distress the ingestion of one or more colchicine tablets is desirable An extended course of colchicine is unnecessary if the attack does not materialize within a few hours If joint symptoms progress and a full blown attack seems imminent colchicine should be continued without interruption until an adequate amount has been taken The desirability of continued vigilance is the thought to be stressed Furthermore it is expedient for the patient to have considerable insight into the vagaries of the prodromata and to anticipate the full development of an acute attack Many times the physician is not available for consultation and the patient should be instructed to proceed without immediate professional advice It is no exaggeration to state that a few hours delay in beginning the ingestion of colchicine may determine the severity as well as the duration of acute episodes of gouty arthritis

Diets recommended for gouty patients are almost as numerous as students of the disease Each kind of foodstuff has been condemned and prohibitions imposed by some physicians as well as praised and recommended by others The conclusions of Ewart[37] are illustrative 'In gout more than elsewhere because of its idiosyncrasies we should beware of dogmatism Gout is undoubtedly prevented by starvation yet it does not follow that it may be cured on this plan Gout may also be prevented by strict avoidance of animal food This does not prove that it need in every case be treated on vegetarian principles Again although gout may fail to attack some of those whose diet is exclusively animal we are not warranted in prescribing meat as the diet for gout Each case should be studied on its own merits In the first edition of the Principles and Practice of Medicine[115] Osler

cautioned against the use of carbohydrates in gout as follows The conversion of azotized food is more complete with a minimum of carbo hydrates than it is with an excess of them — in other words one of the best means of avoiding the accumulation of lithic (uric) acid in the blood is to diminish the carbohydrate rather than the azotized foods Meat of all kinds except perhaps the coarser sorts such as pork and veal and salted ones may be used Fats are easily digested and may be taken freely Epstein[a] recommended a diet high in fats mod erate in proteins and low in carbohydrates Others[b] caution against the dangers of fat and recommend a high carbohydrate diet

The prohibitions against protein and fat are based upon incomplete experimental studies unconvincing clinical data prejudice or empiricism Protein foods were considered harmful because they contain purine bodies It is implied therefore that the intake of a moderate quantity of purines might precipitate an attack of gout or at least worsen the gouty state The fact is overlooked however that proteins and those nucleoproteins which yield pyrimidin bases form urea as the nitrogenous end product and not urate The harm of a moderate protein intake has been emphasized innumerable times but has never been substan tiated by controlled observations Controlled studies should be col lected with patients on a constant metabolic regimen for a long period of time Short periods are apt to be deceptive and prove little We have made an attempt on some of our patients to collect controlled observations Patient No 78 was observed for more than 7 months on the metabolic ward at the Massachusetts General Hospital He was given a low protein low purine diet throughout the period and had severe gout on twenty seven days and twelve acute attacks of arthritis In the following eight months at home he consumed a diet of his own selection without restriction of purine or protein substances and had severe gout on eighteen days Colchicine was the only medicine pre scribed during both periods This suggests that a moderate protein in take did not increase the incidence of acute attacks neither did a low purine intake prevent them

Similar observations were obtained from patient No 74 During a period of nine months in the hospital on a low purine diet he suffered from twenty one attacks of acute gout and spent thirty nine days in bed because of them He was allowed colchicine for acute symptoms only and from 40 to 60 grains (2 6 to 4 gm) of acetylsalicylic acid daily Following discharge he went home on an average house diet This included red meat at least once a day and moderate quantities of beer and hard liquor He had seven acute attacks and spent seven days

in bed during a period of fourteen months. Following the second period he began a third which lasted twenty six months. He took 3 colchicine tablets daily and varying amounts of acetylsalicylic acid. Again he had only seven attacks of acute gout and spent eight days in bed. There appeared to be no greater progression of articular changes during the liberal purine regimen at home than during the low purine regimen in the hospital. Statistically the number of attacks per year and days spent in bed on a low purine intake was nearly tenfold that observed while the patient was eating a liberal portion of meat every day. This is interpreted as meaning that the purine content of the diet is not an important factor in precipitating acute attacks of gout.

The supposed harm of a high fat diet is related in part to observations made nearly 20 years ago. Harding[65] found that a high fat intake increased the urate content of the blood while Lennox[93] noted that starvation with ketosis has a similar effect. In applying these findings to the treatment of gout Lockie and Hubbard[99] discovered that an excessively high fat intake might precipitate an acute attack of gouty arthritis. It seemed reasonable therefore to recommend a diet which contained as little as 30 grams of fat. While many physicians will agree that an excessively high fat intake is unbalanced and undesirable the harm of an adequate fat intake is believed to have been unduly exaggerated.

Foods high in content of purines (Table IX) such as liver, kidneys,

TABLE IX

URATE CONTENT OF CERTAIN FOODS

Item	Urate content mgm per 100 grams
Meat extract	2 000
Calf brains	1 000
Anchovie, sardines, herring	350
Spleen	280
Liver	260
Kidney	240
Pigeon	210
Tongue	170

thymus, pancreas, anchovies, sardines and brains had best be avoided at all times. Not that it has been shown experimentally that any or all of these articles precipitate an attack of gout or influence unfavorably the course of the disease, but because it is difficult to disregard completely

the seasoned dictum that all animal foods are harmful. We have never recommended a low protein or a scrupulously low purine intake in the treatment of our patients except to those who have a sufficient degree of renal insufficiency to have produced azotemia. An otherwise adequate protein intake for patients with advanced renal impairment imposes a burden on the kidneys to excrete urea that is detrimental. A gouty patient in exceptional instances will note a close association between the intake of a particular protein and an acute attack of gout. Avoidance of the offender is advised if this sequence of events is repeated. In the absence of suggestive data a diet balanced in content of fat, protein and carbohydrate is advised. If the sum of the various prohibitions that are recommended by some physicians were imposed a patient might become deficient in essential fatty acids, essential amino acids, iron, fat soluble vitamins and vitamins of the B complex.

A liberal intake of fluids is important in the treatment of interval gout. Spas and watering places of previous generations made a real contribution because of the custom of insisting upon copious imbibition of alkaline waters. The qualitative mineral constituents were probably less important than the quantity of alkaline fluid consumed daily. The famous gichtwasser of Wiesbaden[15] probably has few advantages over many other less notable waters. If a large amount of fluid is available for excretion and the tubules are not forced to reabsorb essentially all of the glomerular filtrate, precipitation of urate in the renal tubules is inhibited. Brøchner-Mortensen[11] showed that as the urine volume increased up to 1 c.c. per minute or approximately 1,500 c.c. per day, the quantity of urate excreted increased also. An increase in urine output beyond this quantity had little effect in increasing urate excretion or urate clearance. A minimum fluid output probably should approximate 2 liters per day. If mineral waters are not taken, the urine may be kept relatively alkaline[101] by the ingestion of a few grams of sodium bicarbonate or sodium citrate daily. Coffee, tea and cocoa need not be restricted. They contain xanthine bases which are not precursors of uric acid[106].

The alcoholic content of fluids should be regulated by rules of temperance rather than abstinence. Probably the most harm from the consumption of alcohol stems from the quantity imbibed rather than the type or quality of the beverage. We have not observed any particular beverage or group of beverages to be an offender in an appreciable number of gouty patients. The port wine drinking habits of our ancestors as a cause of gout is a delusion firmly rooted in the public mind.[107] A few patients sense the close association between

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consumption of a particular potion and the onset of acute joint symptoms Avoidance of this drink is recommended under such circumstances

There are two drugs that are useful in the treatment of intercritical gout They are salicylates and colchicine Salicylates have a place in the modern scheme of gout therapy[8] if it is believed desirable to purge periodically the body of urate We do not believe that a periodic purge has any material effect upon the course of the disease but have been guilty of prescribing it as a substitute for cinchophen for patients who are prejudiced in favor of a cinchophen like substance The ideal experimental substance to rid the body of urate would seem to be diodrast maintained at high plasma levels as discussed in the section on Metabolic Phenomena Unfortunately this is not feasible at present since diodrast is effective only if given parenterally and to maintain high blood levels a total of several hundred cubic centimeters should be injected daily A similar objection holds for salyrgan another drug which enhances urate clearance markedly This leaves a salicylate as Hobson's choice From 30 to 50 grains (2 to 3 3 gm) of salicylate may be taken for several days each week If acetylsalicylic acid is chosen sodium bicarbonate or sodium citrate should be ingested also

Some colchicine should be prescribed in symptom free periods to most gouty patients The action is not specific as it is during an acute attack but the practice nevertheless is believed to be beneficial Garrod[5] maintained that there is some evidence and considerable authority for regarding colchicum as effectual in warding off an attack of gout especially when an approaching fit is beginning A few colchicine tablets should be taken for any gouty aches in the joints Patients who have more than one acute attack a year should take some colchicine regularly This habit may vary from not more than one or two tablets a week to a daily ration of from one to three tablets No untoward effects have been noted from the prolonged ingestion of the drug Tolerance to it does not develop and if an acute attack supervenes a full course of colchicine seems to be as effective as in patients who take it for the first time A patient should never be without a vial of tablets A supply should be available at home at the office and in the travelling kit The age of the patient is no contraindication to the periodic use of colchicine

Cinchophen is not recommended by us either for the treatment of the acute attack or for the treatment of interval periods It is appreciated fully that cinchophen is used enthusiastically by many physicians in many countries Its analgesic properties and ability to augment the

excretion of uric acid in the urine have been verified adequately by clinical and investigative studies The two arguments in its favor however are believed to be offset by several contraindications It is neither a specific for gout nor is it indispensable in the treatment of gout Cinchophen may be toxic if given in large amounts to some patients while in others it may touch off an idiosyncrasy if given in smaller amounts Death from acute liver damage has followed the ingestion of less than 100 grains (6 6 gm) of the drug[118] There is no safe method for the administration to such patients Modified cinchophen preparations such as neocinchophen are equally toxic if given in doses adequate to alter urate clearance quantitatively similar to cinchophen Colchicine with or without an analgesic depending upon the severity of symptoms is as useful in controlling acute articular symptoms as is cinchophen Finally salicylate enhances urate excretion quite as effectively as cinchophen (Table VIII) and according to Jennings[8] is as efficient in controlling pain The attempt of the Food and Drug Administration to reduce the annual consumption of cinchophen in this country deserves the support of all cautious physicians

Treatment of Chronic Deforming Gouty Arthritis

Acute attacks of gouty arthritis may appear in patients with advanced deforming changes as well as in patients suffering from milder forms of the malady A full course of treatment is indicated when they develop Low grade symptoms may persist at other times in spite of apparent adequacy of treatment of the acute episodes Such symptoms are attributed to extensive structural damage rather than to mild incipient acute attacks Colchicine and salicylates are useful in their treatment One or two tablets of colchicine should be taken daily continuously and from 15 to 30 grains (1 to 2 gm) of salicylate daily may be taken periodically Exercise is to be encouraged if the joints will permit it Heat and massage have been of little value in our experience Medical treatment has little to offer beyond these recommendations

Surgical treatment on the other hand which has no place in the handling of the acute attack may be of great help in the rehabilitation of chronically deformed joints There is little in the literature regarding the surgical treatment of chronic gouty arthritis and the possibilities have not been explored extensively The opinion expressed by Duckworth[79] in 1896 is indicative of the prevailing sentiment Any surgical interference with joints affected with concretions or with late arthritic changes has always been regarded with disfavor It must be admitted

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hat many surgical questions which had been considered closed need to be reopened and to be looked at again from the altered standpoint of antiseptic surgery Gout will probably not form an exception to this From 1835 to 1935 only 7 patients were operated upon at the Massachusetts General Hospital for the removal of urate deposits Between the years 1935 and 1941 however more than 50 operations have been performed on osseous and subcutaneous tophi of 12 gouty patients The ages of the patients operated upon ranged from twenty to eighty Three were in the 8th decade of life Less than 10 per cent of the patients seen by us in the past have been considered to be suitable subjects for operative procedures This percentage probably will be increased in the future and less extensive deposits well may be deemed suitable for surgical treatment with the experience of this first series as a basis All of the operations were done by Dr R R Linton or under his immediate supervision Many of the conclusions concerning surgical treatment of gout are taken from his unpublished notes

Surgical Treatment — The indications for surgical treatment are (1) Large subcutaneous tophi which have become unsightly and require removal for cosmetic reasons rather than because of symptoms which they produce Small tophi of the hands or feet which interfere with the wearing of gloves or shoes belong in this group (2) Painful tophi in exposed areas of the body such as those which involve the olecranon bursæ knuckles and the terminal phalanges of the fingers toes and heels (3) Deposits which interfere with movement of the fingers and hands from involvement of extensor or flexor tendons (4) Any discharging sinus associated with a tophaceous deposit (5) Extensive osseous involvement of the fingers or toes

The successful operative results were attributed to the adherence to certain rules that evolved during the study The incidence of arteriosclerosis among gouty patients young and old is an important factor to be considered Great care should be exercised in order to maintain an adequate blood supply particularly in the lower extremities and to prevent trauma to the parchment thin skin which overlies many tophi Arterial tourniquets are contraindicated for operations carried out on the feet since they may damage an arteriosclerotic artery sufficiently to produce arterial thrombosis and possibly gangrene During the operation the skin is retracted with silk sutures so as to prevent infolding of the edges The incision should not be subjected to unnecessary tension when closed lest sloughing of the skin appear Drainage is unnecessary The wounds healed exceptionally well Sepsis developed at only three operative sites and in each of these instances infection was known to

have been present before the operation The benefits from the local application of a sulfonamide in the operative wound were not investigated in this group of patients It is possible that it may have certain advantages in gouty wounds A plaster splint is applied for immobilization after the operation whenever a tendon or joint has been approached The first post operative dressing is not done until a period of from 10 to 12 days has elapsed

The removal of a subcutaneous tophaceous deposit may be achieved by using one of two procedures The most desirable is complete excision of the tophus with the capsule When this is not possible curettage following exposure is satisfactory The incision of choice on the extremities is a transverse one No disadvantage was noted in incising the skin directly over a tophaceous deposit rather than making the incision at the base in sound skin It is possible to circumvent any ulcerated lesion on the medial side of the metatarsal phalangeal joint of the toe with a racquet type of incision and when the wound is closed there is adequate skin to bring together without tension The surgical procedures on the hands are of necessity more conservative than those on the feet It is important to preserve the fingers in spite of extensive urate infiltration The periosteum and bony shell of the phalanx is preserved in so far as is possible The situation in many instances may seem critical by x ray examination (Fig 33) but a significant amount of bony shell and periosteum usually is evident at operation A useful finger results despite the loss of function of the interphalangeal joint if it is possible to preserve the shell

Removal of tophaceous deposits in the toes without resorting to amputation is also possible if x ray examination shows some remains of the phalanges (Fig 38) Otherwise amputation through the proximal phalanx is the operation of choice The head of the first metatarsal is removed if the great toe is amputated (Fig 16) The end results justified such a radical procedure The patients were able to walk in comfort with practically a normal gait instead of leading a wheel chair existence All of the toes were amputated in a few patients and rehabilitation was most gratifying An especially constructed shoe was developed which had a forked steel shank incorporated between two layers of the sole This type of shoe allowed a normal spring to the patient s gait which would be a serious handicap if it were lacking

If a tophaceous depo it involved an important tendon such as a flexor tendon of the fingers the tibialis anticus or a triceps tendon it was considered important to remove the tophus leaving as much as possible of the tendon When the tendons of the extensors of the fingers

were involved either over the digits themselves or the dorsum of the hand, it was impossible to recognize the tendons in many cases and remnants of them were sacrificed The majority recovered the use and function of the fingers and hands with careful postoperative splinting and rehabilitation

The possible development of postoperative gouty arthritis must be appreciated in planning for any surgical procedure The use of colchicine is recommended in order to avoid a postoperative articular complication The routine procedure as developed in our clinic is 3 colchicine tablets $\frac{1}{120}$ gr (0 5 mgm) each a day for 2 days before operation and a similar amount per day for 3 or more days after operation The incidence of postoperative gouty arthritis among patients treated in this manner was 8 per cent As a control series the records of 18 gouty patients were reviewed for incidence of postoperative gouty arthritis following all types of operative procedures In this group colchicine was given neither before nor immediately after operation The incidence of postoperative gout following 34 operations on the untreated patients was 86 per cent The prophylactic use of colchicine in the prevention of postoperative gout following any type of operation therefore seems justified

Postlude

Perchance the most philosophical way for the sufferer is to take up a treatise of medicine and perusing it attentively note the innumerable ills that flesh is heir to which are infinitely worse than his own And while he ponders over life s uncertainties and recognizes that mankind was created to suffer and endure as well as to rejoice and enjoy if he be a minute philosopher he may conclude his reflections with this corollary as were he not afflicted with Gout he must pay the penalty of living and what can a man live long enough to know except that he is born to die [34]

BIBLIOGRAPHY

1 ALLBUTT T C Gout Oxford Medicine Vol IV Chapt 4 Oxford University Press New York 19 0
2 ARETAEUS The Extant Works of Aretaeus the Cappadocian Translated by Francis Adams New Sydenham Soc London 1856
3 ASCHOFF L In Cowdry Arteriosclero is Macmillan New York 1933
4 AUB J C FAIRHALL L T MINOT A S and REZNIKOFF P Lead poisoning Medicine 19 5 IV 1
5 BAUER W and KLEMPERER F Gout In Duncan G G Diseases of Metabolism Saunders Philadelphia 194
6 BAUER W and SHORT C L The treatment of the arthritides of known origin New England Jour Med 1940 CCXXIII 28
7 BECHOLD H and ZIEGLER J Vorstudien uber Gicht III Biochem Ztschr 1914 LXIV 471
8 BENEDICT S R and BEHRE J A Analysis of whole blood III Determination and distribution of uric acid Jour Biol Chem 1931 XCII 161
9 BERGLUND H and FRISK A I Uric acid elimination in man Acta Med Scandinav 1935 LXXXVI 233
10 BLAUCH M B and KOCH F C A new method for the determination o uric acid in blood with uricase Jour Biol Chem 1939 CXXX 443
11 BRØCHNER-MORTENSEN K Uric acid in blood and urine Acta Med Scandinav 1937 Supp 84
12 BROGSITTER A M Histopathologie der Gelenkgicht Vogel Leipzig 19
13 BROGSITTER A M Diät fur Gichtkranke 3rd Ed Thiemann Stuttgart 1937
14 BRUES A M and COHEN A Effects of colchicine and related substances on cell divi ion Biochem Jour 1936 XXX 1363
15 BRUGSCH T Die Stoffwechselpathologie der Gicht Ztschr f exper Path u Therap 1905 II 619
16 BUDD W Researches on gout Med Chir Tr 1855 XXXVIII 23
17 BURIAN R and SCHUR H Über die Stellung der Purinkorper im menschlichen Stoffwechsel Pfluger s Arch f d ges Physiol 1910 LXXXVII 239
18 BURNETT J C Gout and its Cure 2nd Ed Epps London 1900
19 CAMPBELL H The Salicylic Treatment of Gout Rheumatic Gout Neuralgia and Diabete nd Ed Renshaw London 1879
20 COHEN A Gout Am Jour Med Sci 1936 CXCII 488
21 COHEN A Gout and the negro Southern Med and Surg 1941 CIII 634
COOMBS F S Clinical gout Ohio State Med Jour 1940 XXXVI 951

23 COOMBS F S PECORA L J THOROGOOD E CONSOLAZIO W V and TALBOTT J H Renal function in patients with gout Jour Clin Invest 1940 XIX 525

24 DAS GUPTA S C Genesis of gout its relation to blood pressure and antagonism to tuberculosis Indian Med Rec 1935 LV 97

25 DAVIS N S Jr The cardio vascular and renal relations and manifestations of gout Jour Am Med Assoc, 1897 XXIX 261

26 DEITRICK J E The association of congenital hemolytic icterus and gout Internat Clin 1940 III 264

27 DELPEUCH A La Goutte et le Rhumatisme, Carré et Naud 1900

28 DIEUAIDE F R Personal communication

29 DUCKWORTH D A Treatise on Gout Griffin London 1889

30 DUNCAN A Case of gout in an African negro Edin Med and Surg Jour 1807 III 425

31 EAPEN, K Report on case of chronic advanced gout Malayan Med Jour 1936 XI 117

32 EBSTEIN W and SPRAGUE C Beiträge zur Analyse gichtischer Tophi Virchow s Arch f path Anat 1891 CXXV 207

33 EBSTEIN W Die Natur und Behandlung der Gicht 2nd Ed Bergmann Wiesbaden 1906

34 ELLWANGER, G H Meditations on Gout University Press Cambridge 1897

35 ERICKSON R J A case of Vaquez s disease Canada Med Assoc Jour 1917 VII 817

36 EVELYN K A Stabilized photocolorimeter with light filters Jour Biol Chem, 1936 XX 483

37 EWART W Gout and Goutiness and Their Treatment Baillière Tindall and Cox London 1896

38 FINE M S and CHACE A F The influence of salicylates upon the uric acid concentration of the blood Jour Biol Chem 1915 XXI 371

39 FISCHER E and ACH L Neue Synthese der Harnsaure und ihrer Methyl derivate Deutsch Chem Gesell 1895 XXVIII 2473

40 FISCHER E Untersuchungen in der Puringruppe Springer Berlin 1907

41 FITZ R Three cases with intermittently painful joints splenomegaly and anemia Med Clin North Am 1935 XVIII 1053

42 FOLIN O Unlaked blood as a basis for blood analysis Jour Biol Chem 1930 LXXXVI 173

43 FOLIN O BERGLUND H and DERRICK C The uric acid problem an experimental study of animals and man including gouty subject Jour Biol Chem 19 4 LX 361

44 FOLIN O and DENIS W Diagnostic value of uric acid determinations in blood Arch Int Med 1915 XVI 33

45 FOLIN O and LYMAN H On the influence of phenylquinolin carbonic acid (atophan) on the uric acid elimination Jour Pharm and Exp Therap, 1913 IV 539

46 FLETCHER T B Gout In Osler and McCrae Modern Medicine Vol II nd Ed Appleton Philadelphia 1914

47 GAIRDNER W On Gout Its History Its Cause and Its Cure 3rd Ed Churchill London 1854

48 DE GALANTHA E Technic for preservation and microscopic demonstration of nodules in gout Am Jour Clin Path 1935 V 165

49 GARRISON F H An Introduction to the History of Medicine with Medical Chronology Suggestions for Study and Bibliographic Data 4th Ed Saunders Philadelphia 19 9

50 GARROD A B Observations on certain pathological conditions of the blood and urine in gout rheumatism and Bright s disease Med Chir Trans London 1848 XXXI 83

51 GARROD A B The Nature and Treatment of Gout and Rheumatic Gout Walton and Maberly London 1859

52 GARROD A B A Treatise on Gout and Rheumatic Gout (Rheumatic Arthritis) 3rd Ed Longmans Green & Co London 1876

53 GETTLER A O and LINDEMAN E Blood chemistry of pernicious anemia Arch Int Med 19 0 XXVI 453

54 GOLDRING W CHASIS H RANGES H A and SMITH H W Effective renal blood flow in subjects with essential hypertension Jour Clin Invest 1941 XX 631

55 GOODMAN L and GILMAN A The Pharmacological Basis of Therapeutics Macmillan New York 1941

56 GRAFE E Die Krankheiten des Stoffwechsels und ihre Behandlung Springer Berlin 1931

57 GRANVILLE J M Gout in its Clinical Aspect Churchill London 1885

58 GUDZENT F Physikalisch chemische Untersuchungen über das Verhalten der harnsauren Salze in Lösungen Ztschr f Physiol Chem 1909 LX 38

59 GUDZENT F Physikalisch chemisches Verhalten der Harnsaure und ihrer Salze im Blut Ztschr f Physiol Chem 1909 LXIII 455

60 GUDZENT F Gicht und Rheumatismus Springer Berlin 19 8

61 HADECKE M Harn aurearme Diat Abwechslungsreich und Schmackhaft Suddeutsches Verlagshaus Stuttgart 1935

62 HAGEDORN K Ueber einen Fall aleukamischer Myelose mit Osteosklerose und einer alten Gicht Beitrag zur Frage der aleukamischen Myelose ihren Beziehungen zur perniziosen Anamie und zur Osteosklerose und des Problem Gicht und Leukamie Ztschr f klin Med 19 6 CIV 124

63 HANDERSON H E Gilbertus Anglicus Medicine of the Thirteenth Century Cleveland Med Lib Assoc Cleveland 1918

64 HANZLIK P J Actions and Uses of the Salicylates and Cinchophen in Medicine Williams and Wilkins Baltimore 1927

65 HARDING V J ALLIN K D EAGLES B A and VAN WYCK H B The effect of high fat diets on the content of uric acid in blood Jour Biol Chem 1925 LXIII 37

23 COOMBS F S PECORA L J THOROGOOD E CONSOLAZIO W V and TALBOTT J H Renal function in patients with gout Jour Clin Invest 1940 XIX 525
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36 EVELYN K A Stabilized photocolorimeter with light filters Jour Biol Chem, 1936 XX 483
37 EWART W Gout and Goutiness and Their Treatment Bailliere Tindall and Cox London 1896
38 FINE, M S and CHACE A F The influence of salicylates upon the uric acid concentration of the blood Jour Biol Chem 1915 XXI 371
39 FISCHER E and ACH L Neue Synthese der Harnsaure und ihrer Methyl derivate Deutsch Chem Gesell 1895 XXVIII 2473
40 FISCHER E Untersuchungen in der Puringruppe Springer Berlin 1907
41 FITZ R Three cases with intermittently painful joints splenomegaly and anemia Med Clin North Am, 1935 XVIII 1053
42 FOLIN O Unlaked blood as a basis for blood analysis Jour Biol Chem 1930 LXXXVI 173
43 FOLIN O BERGLUND H and DERRICK C The uric acid problem an experimental study of animals and man including gouty subject Jour Biol Chem 1924 LX 361
44 FOLIN O and DENIS W Diagnostic value of uric acid determinations in blood Arch Int Med 1915 XVI 33
45 FOLIN, O and LYMAN H On the influence of phenylquinolin carbonic acid (atophan) on the uric acid elimination Jour Pharm and Exp Therap, 1913 IV 539

46 FUTCHER T B Gout In Osler and McCrae Modern Medicine Vol II 2nd Ed Appleton Philadelphia 1914

47 GAIRDNER W On Gout Its History Its Cause and Its Cure 3rd Ed Churchill London 1854

48 DE GALANTHA E Technic for preservation and microscopic demonstration of nodules in gout Am Jour Clin Path 1935 V 165

49 GARRISON F H An Introduction to the History of Medicine with Medical Chronology Suggestions for Study and Bibliographic Data 4th Ed Saunders Philadelphia 1929

50 GARROD A B Observations on certain pathological conditions of the blood and urine in gout rheumatism and Bright s disease Med Chir Trans London 1848 XXXI 83

51 *GARROD A B The Nature and Treatment of Gout and Rheumatic Gout* Walton and Maberly London 1859

52 GARROD A B A Treatise on Gout and Rheumatic Gout (Rheumatic Arthritis) 3rd Ed Longmans Green & Co London 1876

53 GETTLER A O and LINDEMAN E Blood chemistry of pernicious anemia Arch Int Med 1920 XXVI 453

54 GOLDRING W CHASIS H RANGES H A and SMITH H W Effective renal blood flow in subjects with essential hypertension Jour Clin Invest 1941 XX 637

55 *GOODMAN L and GILMAN A The Pharmacological Basis of Therapeutics* Macmillan New York 1941

56 GRAFE E Die Krankheiten des Stoffwechsels und ihre Behandlung Springer Berlin 1931

57 GRANVILLE J M Gout in its Clinical Aspects Churchill London 1885

58 GUDZENT F Physikalisch chemische Untersuchungen uber das Verhalten der harnsauren Salze in Lösungen Ztschr f Physiol Chem 1909 LX 38

59 GUDZENT F Physikalisch chemische Verhalten der Harnsaure und ihrer Salze im Blut Ztschr f Physiol Chem 1909 LXIII 455

60 GUDZENT F Gicht und Rheumatismus Springer Berlin 1928

61 HÄDECKE M Harn aurearme Diat Abwechslungsreich und Schmackhaft Suddeutsches Verlagshaus Stuttgart 1935

62 HAGEDORN K *Ueber einen Fall aleukämischer Myelose mit Osteosklerose* und einer alten Gicht Beitrag zur Frage der aleukämischen Myelose ihren Beziehungen zur perniziosen Anämie und zur Osteosklerose und des Problems Gicht und Leukämie Ztschr f Klin Med 1926 CIV 1 4

63 HANDERSON H F Gilbertus Anglicus Medicine of the Thirteenth Century Cleveland Med Lib Assoc Cleveland 1918

64 HANZLIK P J Actions and Uses of the Salicylates and Cinchophen in Medicine Williams and Wilkins Baltimore 1927

65 HARDING V J ALLIN K D EAGLES B A and VAN WYCK H B The effect of high fat diets on the content of uric acid in blood Jour Biol Chem 1925 LXIII 3

66 HARPUDER K Pharmakologische Beeinflussung des Purinstoffwechsels beim Menschen Ztschr f d ges exper Med Berlin 1924 XLII 1
67 HEINE J Uber die Arthritis Deformans Virchow s Arch f path Anat 19-6 CCLX 521
68 HENCH, P S A clinic on some diseases of joints Med Clin North Am 1935 XIX 551
69 HENCH, P S Chronic Arthritis Chronic Infectious Arthritis Chronic Senescent Arthritic Gout In Modern Medical Therapy in General Practice Williams and Wilkins Baltimore 1940
70 HERRICK W W and TYSON T L Gout — a forgotten disease Am Jour Med Sci 1936 CXCII 483
71 HIPPOCRATES The Genuine Works of Hippocrates Translated from the Greek with a Preliminary Discourse and Annotations by Franci Adams Vol I and II Wood New York 1886
72 HIS W Die Ausscheidung von Harnsaure im Urin der Gichtkranken mit besonderer Berucksichtigung der Anfallszeiten und bestimmter Behand lungsmethoden Deutsch Arch f klin Med 1899 LXV 156
73 HORBACZEWSKI J Beitrage zur Kenntniss der Bildung der Harnsaure und der Xanthinbasen sowie der Entstehung der Leucocytosen im Sau gethierorganismus Sitzungsb d k Akad d Wissensch Math naturw Cl Wien 1891 LXXXIII
74 HORMELL R S Notes on the history of rheumatism and gout New England Jour Med 1940 CCXXIII 754
75 HUBBARD R S and FINNER I L The determination of uric acid in blood by the method of Folin and Wu Jour Lab and Clin Med 19 3 VIII 605
76 HUBER Zur Verwertung der Rontgenstrahlen im Gebiete der inneren Medizin Deutsch med Wchnschr 1896 XXII 182
77 HUTCHINSON J On the hereditary transmission of gout Med Times and Gaz 1876 I 543
78 HUTCHINSON J On the importance of perseverance in inquiries as to the inheritance of gout Arch Surg London 1896 VII 197
79 ISAACS R The pathologic physiology of polycythemia vera Arch Int Med 1923 XXXI 289
80 JACOBSON B M The uric acid in the serum of gouty and non gouty individuals its determination by Folin s recent method and its significance in the diagnosis of gout Ann Int Med 1938 XI 1277
81 VON JAKSCH R Ueber Uricacidaemie Deutsch med Wchnschr 1890 XVI 741
82 JENNINGS G H The value of sodium salicylate in the treatment of gout Rep Chron Rheumat Dis 1937 III 106
83 JORDAN E P and GASTON D The blood uric acid in disease Jour Clin Invest 1932 XI 747
84 JOSLIN F P The Treatment of Diabetes Mellitus 5th Ed Lea and Febiger Philadelphia 1935

85 KAHLMETER G Gout In Proceedings of the International Congress on Rheumatism and Hydrology (London and Oxford) and the Bicentenary Congress on Chronic Rheumatism (Bath) p 298 Headley Bro London 1938

86 KINELL J and HADEN R I Gout a review of 6? cases Med Clin North Am 1940 XXIV 4 9

87 KLEMPERER G Zur Pathologie und Therapie der Gicht Deutsch med Wchnschr 1895 XXI 655

88 KNAGGS R L and RODMAN C H Report on the Strangeways s collections of rheumatoid joints in the Museum of the Royal College of Surgeons Brit Jour Surg 1933 XX 1

89 KRAFKA J Jr A neglected factor in the etiology of gout Jour Bone and Joint Surg 1935 XVII 1049

90 KRÜGER M and SCHMID J Die Entstehung der Harnsaure aus freien Purinbasen Ztschr f physiol Chem 1901–0 XXXIV 549

91 LAMBIE C G Study of juvenile gout in patient suffering from chronic erythronoclastic anemia of obscure origin together with observations upon physical state of uric acid in blood and effects of splenectomy Med Jour Australia 1940 I 535

92 LANC F J Gelenkgicht (arthritis urica) Handbuch der spez Path Anat. Hist Part III IX 309 Springer Berlin 1937

93 LENNOX W G Increase of uric acid in the blood during prolonged starvation Jour Am Med Assoc 19 4 LXXXII 60

94 LEVENE P A and BASS L W Nucleic Acids Chemical Catalog Co New York 1931

95 LICHTWITZ L Gout Bull New York Acad Med 1934 X 306

96 LINDSAY J Gout its Etiology Pathology and Treatment Oxford Univ Pres London 1913

97 LITTEN M Pathologisch anatomische Beobachtungen Ein Fall von schwerer Gicht mit Amyloiddegeneration Virchow s Arch f path Anat 1876 LXVI 129

98 LLEWELLYN L L J Gout Heinemann London 1920

99 LOCKIE L M and HUBBARD R S Gout changes in symptoms and purine metabolism produced by high fat diets in four gouty patients Jour Am Med Assoc 1935 CIV 2072

100 LOEWENHARDT F E R Besteht bei der Gicht eine Partialfunktionsstörung der Niere fur die Harnsaureausscheidung Klin Wchnschr 1932 I 2319

101 LONGSTRETH M Rheumatism Gout and Some Allied Disorders Wood and Co New York 1882

102 LUDWIG A O BENNETT G A and BAUER W A rare manifestation of gout widespread ankylosis simulating rheumatoid arthritis Ann Int Med 1938 XI 1 48

103 LUFF A P Gout its Pathology Form Diagnosis and Treatment 3rd Ed Wood and Co New York 1907

104 LUTHJE Ueber Bleigicht und den Einfluss der Bleiintoxication auf die Harnsäureausscheidung Ztschr f klin Med 1896 XXIX 266
105 MAGNUS-LEVY A Ueber Gicht klinische Beobachtungen chemische Blutuntersuchungen und Stoffwechselversuche Ztschr f klin Med 1899 XXXVI 353
106 MENDEL L B and WARDELL E L Effect of ingestion of coffee tea and caffein on the excretion of uric acid in man Jour Am Med Assoc 1917 LXVIII 1805
107 MINKOWSKI O Die Gicht A Holden Wien 1903
108 MONROE R T The detection of gout Med Clin North Am 1935 XVIII 999
109 MOORE N Some observations on the morbid anatomy of gout St Barth Hosp Rep London 1887 XXIII 289
110 VON MULLER F Ueber die uratische Diathese Wien klin Wchnschr 1937 L 1291
111 MUNK F Zur Pathologie und pathologischen Anatomie der Gicht Deutsch med Wchnschr 1920 XLVI 204
112 MYERS V C and FINE M S The non protein nitrogenous compound of the blood in nephritis with special reference to creatinine and uric acid Jour Biol Chem 1915 XX 391
113 NICOLAIER O and DOHRN M Ueber die Wirkung von Cholincarbonsäure und ihrer Derivate auf die Ausscheidung der Harnsäure Deutch Arch f klin Med, 1908 XCIII 331
114 OSGOOD R B The medical and social approaches to the problem of chronic rheumatism Am Jour Med Sci 1940 CC 429
115 OSLER W The Principles and Practice of Medicine D Appleton and Co New York 1892
116 OWEN T K and ROBERTS J C Acholuric jaundice and gout Brit Med Jour 1937 II 661
117 PAGET J Additional cases of osteitis deformans Med Chir Trans 1882 LXV 225
118 PALMER W L WOODALL P S and WANG K C Cincophen and toxic necrosis of the liver a survey of the problem Trans Assoc Am Phys 1936 LI 381
119 PEARSON G Experiments and observations tending to show the composition and properties of urinary concretions Phil Trans London 1798 LXXXVIII 15
120 PELLETIER and CAVENTOU Examen chimique de plusieurs végétaux de la famille des colchicées et du principle actif qu ils renferment Ann Chim Phys 1920 XIV 69
121 PETERS J P and VAN SLYKE D D Quantitative Clinical Chemistry Methods Williams and Wilkins Co Baltimore 1932
122 POMMER G Mikroskopische Unterschungen über Gelenkgicht Fischer Jena 1929
123 POMMER G Von den Fruhstadien und den Ruckbilddungsbefinden der

gichtischen Harnsalzablagerungen Beitrage z path Anat und z allgem Path 1933 XC 513

124 PRATT J H A study of the uric acid in the blood in gout by the method of Folin and Denis Trans Assoc Am Phys 1913 XXVIII 387

125 REICHE F Die Harnsaure im Blut und Liquor und in pathologischen Flussigkeiten Ztschr f klin Med 1933 CXXV 56

126 RINDFLEISCH L Über Bildung und Ruckbildung gichtischer Tophi Virchow s Arch f path Anat 1903 CLXXI 361

127 ROCKWOOD F W The elimination of endogenous uric acid Am Jour Physiol 1904–05 XII 38

128 ROOSE R *Gout and its Relation to Diseases of the Liver and Kidneys* 3rd Ed Lewis London 1887

129 ROSENBERG E F Gout and male hermaphrodism report of a case Proc Staff Meet Mayo Clinic 194 XVII 300

130 ROSENBLOOM J The blood pressure in gout Jour Am Med Assoc 1918 LXX 2000

131 RUTLEDGE D I and BEDARD R E Criteria for diagnosis of presumptive (pretophaceous) gout management of an illustrated case Proc Staff Meet Mayo Clinic 1937 XII 149

132 SCHADE H Laws of uric acid colloid Ztschr f klin Med 1922 XCIII 1

133 SCHEELE K W Examen chemicum calculi urinarii Opuscula II 73 Leipzig 1776

134 SCHIRMER K H Die Paget sche Knochenerkrankung (kritischer Sammelbericht) Zentralbl f d Grenzgeb d Med u Chir 1908 XI 561

135 SCHMIDT M B Kaltmetastase und Kalkgicht Deutsch Med Woch 1913 XXXIX 59

136 SCHMIDT M B Ablagerung harnsaurer Salze In von Krehl und Marchand Handbuch der allgemeinen Path Chapter V Vol III section 2 266 Hirzel Leipzig 1921

137 SCHNITKER M A A history of the treatment of gout Bull Inst History of Med 1936 IV 89

138 SCHNITKER M A and RICHTER A B Nephritis in gout Am Jour Med Sci 1936 CXCII 241

139 SCUDAMORE C *A Treatise on the Nature and Cure of Gout* 4th Ed London 18 3

140 SEE G Etudes medicales sur l acide salicylique et les salicylates Bull d l Acad d Med 1877 VI 689

141 SNAPPER I and GRÜNBAUM A The non excretory functions of the kidney In *The Kidney in Health and Diseases* Berglund and Medes Lea and Febiger Philadelphia 1935

142 SMITH H W *The Physiology of the Kidney* Oxford Univ Press New York 1937

143 SMITH H W GOLDRING W CHASIS H and RANGES H A Observations on the effective renal blood flow and functional excretory mass in man with special reference to essential hypertension Am Jour Physiol 1938 CXXIII 189

144 SMYTH C J and FREYBERG R H A study of the hereditary nature of gout a report of two families Ann Int Med 1942 XVI 46
145 STOKVIS B J Over het ureum als onmiddellijke of middellijke oozaak der zoogenaamde uraemische verschijnselen Nederl Tijdschr v Geneesk 1860, IV 513
146 STRIEKLIN Quoted by Peters and Van Slyke reference 121
147 SYDENHAM T The Whole Works of That Excellent Practical Physician Dr Thomas Sydenham translated by John Pechey 7th Ed Feales London 1717
148 TALBOTT J H JACOBSON B M and OBERG S A The electrolyte balance in gout Jour Clin Invest 1935 XIV 411
149 TALBOTT J H and SHERMAN J M Urate distribution in blood Jour Biol Chem 1936 CXV 361
150 TALBOTT J H and COOMBS F S Metabolic studies on patients with gout Jour Am Med Assoc 1938 CX 1977
151 TALBOTT J H and COOMBS F C Concentration of serum uric acid in non affected members of gouty families Jour Clin Invest. 1938 XVII 508 proceedings of 30th annual meeting of Am Soc. Clin Investigation held in May 1938
152 TALBOTT J H Serum urate in relatives of gouty patients Jour Clin Invest 1940 XIX 645
153 TALBOTT J H Clinical gout Rocky Mt Med Jour 1941 XXXVIII 18?
154 TALBOTT, J H The treatment of gout Bull New York Acad Med 1942 XVIII 318
155 TALBOTT J H Gout In Stieglitz Geriatrics Saunders and Co Philadelphia 1943
156 TAYLOR G D FERGUSON A D and KASABACH H and DAWSON M H Roentgenologic observations on various types of chronic arthritis Arch Int Med 1936 LVII 979
157 THANNHAUSER S J Lehrbuch der Stoffwechsels und der Stoffwechselkrankheiten Bergmann Munchen 1929
158 THUDICHUM J L W A Treatise on the Pathology of the Urine Including a Complete Guide to its Analysis 2nd Ed Churchill London 18??
159 UMBER F Ernahrung und Stoffwechselkrankheiten Urban und Schwarzenberg Berlin 1925
160 VIRCHOW R Seltene Gichtablagerungen Virchow s Arch f path Anat 1868 XLIV 137
161 VORHAUS M G and KRAMER M I Studies of thiamin chloride in gout Trans Am Therap Soc 1938 XXXVIII 109
162 WIECHOWSKI W Ueber die Zersetzlichkeit der Harnrohre im menschlichen Organismus Arch f exper Path u Pharm 1909 LX 185
163 WEIL M P Heredite des goutteux Presse Med 1934 XLII 701
164 WEINTRAUD W Die Behandlung der Gicht mit Phenylchinolincarbonsaure (Atophan) nebst Bemerkungen uber die diatetische Therapie der Krankheit Therap d Gegenwart 1911 XIII 97

165 WESTENHOEFFER Die Konservierung harnsaurer Niederschlage in Organen Verhandl Deutsch path Gesellsch 1904 VII 259
166 WEVE H J M Over keratitis urica en andere vormen van jichtig ooglijden Van Hengel Rotterdam 19 4
167 WILDE R R The Physiology of Gout Rheumatism and Arthritis Wright London 19 1
168 WOLLASTON W H On Gouty and Urinary Concretions Phil Trans London 1797 LXXXVII 386

CHAPTER V

DIABETES MELLITUS

BY ALEXANDER MARBLE

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Definition

Diabetes mellitus is an inheritable disease of metabolism characterized by the inability of the body to utilize and store carbohydrate in a normal fashion with the result that the concentration of glucose in the blood increases and this sugar appears in the urine These abnormalities arise because of the diminished secretion or diminished effectiveness of insulin produced by the beta cells of the islands of Langerhans of the pancreas. Despite the dominant role of the pancreas influences arising in other endocrine glands especially the pituitary and adrenals, and in the liver are of great importance Metabolic disturbances are not confined to carbohydrate, in uncontrolled diabetes there is an excessive breakdown of protein with an increased excretion of nitrogen in the urine, fats likewise are broken down to an abnormal degree to furnish energy When the ketone bodies resulting from the catabolism of fat are in excess of the ability of the tissues to utilize them they accumulate in the blood and are found in the urine A state of acidosis then is said to be present which if unchecked progresses to coma and death

Prevalence

Diabetes is not an uncommon disease and realization of its importance is growing As a cause of death in the United States diabetes advanced from twenty seventh place in 1900 to eighth place in 1943 Excluding accidents and prematurity it ranked seventh in 1948 Among white females over 45 years of age diabetes was fifth among the causes of death in 1943 Even these impressive figures do not tell the whole story With improved methods of treatment most diabetics are living longer and longer and dying at later ages not of diabetes but of other diseases Physicians in recording the causes of death on death certificates often omit a concomitant diabetes This tendency is so great that probably one fourth to one third of deaths among diabetics escape listing as such For example when Joslin and Lombard[1] examined the death certificates of 744 known diabetics they found that in only 75 9 per cent was diabetes mentioned A similar study subsequently of 1 000 patients revealed that in only 76 5 per cent was diabetes mentioned on the death certificate[2] Palmer[3] reported a similar experience from the state of Washington

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[illegible] 1941 to 38,638 in 1948 with crude [illegible] from 25 4 to 26 4 As [illegible] death rates are more stable [illegible] the long term trend of

[illegible] RATES PER 100 000 FROM [illegible] GENERAL POPULATION [illegible] STATES

[illegible] (Metropolitan Life Insurance Co) [illegible] supplied by him)

		Crude
[illegible]	[illegible]	28 5*
[illegible]	[illegible]	26 4
[illegible]	[illegible]	26 2
[illegible]	[illegible]	4 8
[illegible]	[illegible]	26 6
[illegible]	[illegible]	6 5
[illegible]	[illegible]	22 3
[illegible]	[illegible]	19 1
[illegible]	[illegible]	16 8
[illegible]	[illegible]	16 1
[illegible]	[illegible]	17 6
[illegible]	[illegible]	15 3
[illegible]	[illegible]	14 1
[illegible]	[illegible]	11.0

[illegible] Total U S. 1933 1949
[illegible] total population of the United States
[illegible] certificates
[illegible] International List of Causes of Death The provisional
[illegible]

[illegible] has been upward Bearing in [illegible] one third of the individuals dying [illegible] it seems likely that considerably [illegible] with although not necessarily of [illegible]

[illegible] only a partial answer as to the [illegible] in the country Various attempts have [illegible] by surveys among the living [illegible] Public Health Service carried out a [illegible] gain some idea of the magnitude of [illegible]

the chronic disease problem in the United States. In a house-to-house canvass a survey was made of some [illegible] 500 000 persons in 700 000 households. On the basis of the data obtained it was estimated that there were in the United States in 1937 about 660 000 persons with diabetes[5]. Marks[4] points out that one must make a distinction between the number of known diabetics and the total number with the disease, including cases as yet undiagnosed. He estimates known diabetics in the United States at about 700 000 in 1946 and the number of new cases diagnosed annually as at least 55 000. He estimates that 2.1 per cent of the males and 3.8 per cent of the females in our present population eventually will become diabetic.

The above-cited estimates of known diabetics may be low. Moreover, data recently acquired suggest that the number of undiagnosed cases may be large indeed. In a study which included 69 088 selectees in World War II aged 18 to 37 years, Blotner[6] found that approximately [illegible] per cent had either clinical diabetes or sugar tolerance tests indicating impairment to a degree usually accepted as diagnostic of diabetes. Furthermore, Wilkerson and Krall[7] of the United States Public Health Service found 70 cases of diabetes, 40 previously known and 30 newly discovered, in a survey of Oxford, Massachusetts. In this town with a population of 4 983, urine and blood sugar tests were carried out in 3 516 persons. From the results it was estimated that the prevalence of diabetes in Oxford was 1.7 per cent. If one takes a lower figure and assumes that 1 to 1.5 per cent of the population has diabetes, then the total in the country today would amount to 1.5 to over [illegible]o million persons. Therefore there is justification for the statement of the American Diabetes Association in its annual Diabetes Detection Drive that there are probably about a million known and another million unrecognized diabetics in the country. In the latter group there are, of course, many mild, relatively asymptomatic cases.

There has been much written and said regarding the variation in incidence of diabetes in certain races, countries and climates. For example, it has long been stated that diabetes is less common in the colored race, that it is less common in the southern states of the United States, and that it is less common in certain countries throughout the world, particularly those with tropical climates. The best evidence indicates, however, that diabetes is universal, and that if the same care and zeal are used in the ferreting out, diagnosing and recording of cases, reported differences in incidence become less. Certain influencing factors must, of course, be taken into account. In addition to close

dying with diabetes has varied from 33,879 in 1941 to 38,638 in 1948 with crude rates per 100,000 population of from 25 4 to 26.4 As shown in Table I, although age-adjusted death rates are more stable than crude rates, there is no doubt but that the long term trend of

TABLE I

CRUDE AND AGE ADJUSTED DEATH RATES PER 100 000 FROM DIABETES MELLITUS IN THE GENERAL POPULATION OF THE UNITED STATES

(Adapted by permission from article by Marks[4] (Metropolitan Life Insurance Co) and from data later supplied by him)

Year	*Adjusted*[b]	*Crude*
1949 (provisional)[c]	—[d]	28 5[e]
1948	24 3	26.4
1947	24 2	26 2
1946	23.0	24.8
1945	24 1	6.6
1940	26 5	6 5
1935	24 3	22 3
1930	22 2	19.1
1925	0 3	16.8
1920	19.8	16 1
1915	21 5	17.6
1910	18 9	15 3
1905	17.0	14 1
1900	13.0	11.0

Expanding Registration Area 1900 to 1932 Total U S 1933 1949
[b] Adjusted on basis of age distribution of the total population of the United States enumerated in 1940
Based upon a 10 per cent sample of death certificates
[d] Not available
Based upon 5th revision of International List of Causes of Death The provisional rate by the 6th revision is 16 5

diabetes mortality in the United States has been upward Bearing in mind that probably one fourth to one third of the individuals dying with diabetes escape listing as such, it seems likely that considerably more than 50 000 persons die yearly with, although not necessarily of diabetes

A study of mortality statistics gives only a partial answer as to the number of persons with diabetes in the country Various attempts have been made to arrive at the incidence by surveys among the living Thus in 1935-1936 the United States Public Health Service carried out a National Health Survey in order to gain some idea of the magnitude of

racial group and the greater tendency to intermarriage, thus accentuating the influence of heredity.

Not so well appreciated is the higher incidence among certain other racial groups. For example diabetes is relatively frequent among the Irish living in the United States. Diabetes is said to be infrequent in China but truly adequate statistics are lacking. It was once supposed that diabetes was almost non-existent among negroes but in recent years it has become apparent that the disease is fully as prevalent in the colored race as in the white if statistics are taken from areas in which the negro population is urbanized and has easy access to medical facilities.

Etiology

Heredity

There is much evidence to indicate that the tendency to diabetes is inheritable. The idea is not new, having been advanced as early as the 7th century A.D. Morton discussed it at some length in 1696. Among the 6,357 patients seen between 1897 and 19 8 by Joslin and associates[4] and studied by the Statistical Bureau of the Metropolitan Life Insurance Company a family history of diabetes was secured in 4.5 per cent. Among 1,619 diabetics treated at the New England Deaconess Hospital during 1941 the incidence of heredity was 41 per cent and in those with onset of under 15 years was 49 per cent. Among 2,191 patients with onset of diabetes in childhood there was an hereditary influence in 35 per cent, and among the 40 erstwhile children with a duration of diabetes of 20 or more years the percentage was 5[illegible] per cent. In favor of the conception that the tendency to diabetes is inherited Pincus and White[7] reported the following: (1) the almost simultaneous occurrence of diabetes in both members of pairs of similar twins; (2) the greater incidence of diabetes in the blood relatives of a diabetic than in those of a control population; (3) the demonstration that Mendelian ratios of the recessive type are found in a large series of cases selected at random; (4) the demonstration of expected ratios in presumably latent cases. They found that among at least 16 of 33 sets of similar twins both were diabetic (48.5 per cent), whereas in only 2 (3.2 per cent) of 63 pairs of dissimilar twins did each twin have the disease. Assuming that the tendency to diabetes is inherited as a recessive Mendelian trait, then one may predict that if both parents have diabetes the offspring almost

medical supervision and accurate reporting of morbidity and mortality, the incidence of diabetes would be highest where obesity is most frequent, where the percentage of females is highest, where the average age of the population is greatest, and where the percentage of certain racial groups is highest.

Age Incidence

Diabetes is a disease chiefly of middle and later life. In a study of a large group of patients it was found the most common age at onset was 51 years among males and 55 among females.* The most favored period of onset is between the ages of 45 and 60 years. Diabetes is relatively rare in children; before the age of 15 years probably only one person in about 2,000–2,500 has diabetes.

Sex Incidence

Diabetes is much more common among adult females than among adult males. In 1940 in the United States the mortality per 100,000 was 20.0 for males and 34.3 for females. Females predominated from the age of 35 on, and there were nearly twice as many females as males with diabetes between the ages of 45 and 74. At the age of 65 and over diabetes is known to exist in at least 1 of every 45 women in the United States as compared to 1 of 70 men.

Race Incidence

The relatively high incidence of diabetes among Jews has long been commented upon. Among 5,000 patients seen at the George F. Baker Clinic in Boston, Jews constituted 16.2 per cent, a proportion obviously far greater than that of Jews in the general population in the area of the country from which this experience is drawn. Two possible explanations come to mind, the higher incidence of obesity in this

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* Throughout this article when no other source is given for specific data it will be understood that statistics and experience of The George F. Baker Clinic, New England Deaconess Hospital, Boston (Elliott P. Joslin, M.D., and associates) are being quoted.

Infections

Infections have been held by many to be a cause of diabetes It is of course a matter of common experience that once diabetes has been established infections often cause a temporary flare up in the severity of the disease with an increase in the insulin requirement However the evidence in favor of infections causing diabetes is not convincing and it is likely that the reported cases in which diabetes has seemed to be due to an acute infection actually have been instances in which the infection has led to diagnostic studies hitherto not carried out or in the unusual case has brought to the fore a latent diabetes In the experience of the writer and his associates infection has not been found to precede diabetes in any convincing number of cases Infections are common in childhood and yet the disease is rare in this age group It is obvious that infection or inflammation of the pancreas i e pancreatitis might result in a temporary or even permanent disturbance of carbohydrate metabolism but as a matter of actual practice the number of such cases is extremely small[10]

Trauma

There are likewise many who believe that trauma both of nervous or mental and physical nature can precipitate diabetes Such a conception not infrequently is presented in courts of law in cases in which an individual has suffered an injury and is found on study to have diabetes The argument is brought forward that a blow on the head or elsewhere on the body is responsible for the production of diabetes Such a view is not supported by the best evidence There is little or nothing to indicate that diabetes may result from physical or nervous trauma The world literature contains only a very few well documented cases and even these do not stand the test of careful scrutiny[11] One must assume that in the usual situation the injured individual has had unrecognized diabetes for some time and that the chief contribution of the trauma is to bring the person under medical supervision where accurate studies are carried out including those of the blood and urine for sugar It is of course possible that trauma might bring into the open a latent and hitherto asymptomatic diabetes Theoretically direct trauma to the pancreas with sufficient injury to island of Langerhans could cause diabetes but this is a remote possibility since the pancreas is so located

certainly will develop it, if permitted a sufficient life span. If one parent has diabetes and other has not, but if the father or the mother of the non-diabetic parent has it, the child has a 50 per cent chance of developing diabetes, since one parent is a diabetic and the other is a carrier. If neither parent has diabetes, but if the disease has occurred in a parent of each of them, both are carriers and the offspring have a 25 per cent chance of developing diabetes. If one parent has diabetes and the other is a non-diabetic with no trace of diabetes in relatives, none of the offspring should have diabetes although they will, of course, be carriers and would pass the tendency for development on to their children.

Space does not permit a more detailed discussion of this problem, but the evidence in favor of the hereditary character of diabetes is overwhelming. If, for the sake of this discussion, one assumes that almost all, if not all, diabetes is inherited, then presumably from one fourth to one third of the population inherits such a tendency, and this estimate is borne out by surveys among population groups selected at random. However, it is likely that no more than 1.5 to 2.0 per cent of the population has diabetes. What then are the factors which precipitate diabetes in the predisposed? This is a subject about which relatively little of definite nature is known, although there is ample basis for intelligent speculation.

Obesity

Perhaps the most prominent influencing factor is that of obesity, although it is not clear whether obesity helps in precipitating diabetes or whether both obesity and diabetes are favored by some other factor of endocrine (such as pituitary) origin. Whatever the truth may be in this regard, the fact remains that most middle-aged and elderly diabetics are overweight and often grossly so prior to the onset of the disease. In the experience of Joslin and associates[8] among 4,596 patients aged 20 and over for whom facts were available, 78.5 per cent of the males and 83.3 per cent of the females were 5 per cent or more above the average weight for age and height at the time of their maximum weight. Of the men 16.5 per cent and of women 25.8 per cent were 40 per cent or more overweight at their maximum. In Jewish adult patients the tendency to obesity is even more marked than in other patients. Among children, in contrast to adults, overweight prior to onset usually is not present, but its place often is taken by overheight.

the onset of diabetes occurs with great frequency in women at or near the menopause and in children the curve of age at onset has a peak at puberty These facts gleaned from clinical observations are strong hints that in the human patient the precipitation of diabetes may represent the result of a complex disturbance in the glands of internal secretion In recent years many investigations along these lines have been made in experimental laboratories A summary of these interesting and important studies will be given in the following section

Pathological Physiology

Although work in recent years has brought us closer to the answer we do not as yet know the basic defect in diabetes It is obvious that the diabetic man or animal cannot utilize glucose in the normal fashion The glucose of the blood remains elevated and is not stored in normal fashion in the liver muscles and skin Sugar is wasted in the urine All of these abnormalities can be corrected if insulin is given parenterally so that the assumption is valid that the efficiency of the pancreas is all important However despite these well established facts of great clinical importance the exact nature of the metabolic defect and the exact site of action of insulin remain obscure although these matters are becoming clearer as time goes on

'Overproduction' vs 'Underutilization'

Among those interested in diabetes there has been for several decades a conflict of views as to the nature of diabetes Many workers believe that in diabetes the tissues are unable to oxidize glucose or at any rate that lessened ability to oxidize glucose is the basic difficulty in diabetes This underutilization theory has been opposed by those who believe that the tissues actually possess the power of oxidizing carbohydrate but that the chief difficulty is one of overproduction of glucose from both carbohydrate and non carbohydrate sources The results of certain experiments in animals with the pituitary and adrenal glands and their extracts to be discussed later have been interpreted as lending support to the overproduction theory Soskin[1] regards carbohydrate metabolism as a dynamic balance between blood sugar formation in the liver and its utilization in the body tissues

in the center of the abdomen that any injury extensive enough to destroy more than nine-tenths of the organ probably would result in loss of life. Conceivably also, by virtue of release of diabetogenic influences of pituitary and adrenal origin, the "alarm reaction" occasioned by *severe trauma with shock might cause a temporary flare up in a known* diabetic or cause a latent diabetes to become manifest. However, there is no evidence to indicate that such a train of events will truly initiate diabetes.

The best argument against the neurogenic and traumatic origin of diabetes is to be found in the experience in World Wars I and II. Here millions of men were engaged in battle under conditions of extreme mental, nervous and physical strain over days, weeks and months of time. By Selective Service they had been drawn from the general population among which it is known that at least one fourth of persons have diabetes in relatives. Despite this, the incidence of development of diabetes among the armed forces was strikingly low and no more than one would have anticipated under normal conditions in the population group concerned.

Other Influences

The influences of age, sex and race in the development of diabetes have been touched upon already. The influence of *climate* is difficult to assay and probably not of fundamental importance. Obesity and therefore possibly diabetes may be favored by *sedentary occupations* and the use of power machinery rather than hand labor. Patients often ask whether diabetes may be produced by eating a high carbohydrate diet as sugar, sweets, pastries and foods rich in starch. There is no good evidence to indicate that such is true except as such eating habits may favor obesity.

In recent years data have accumulated to indicate that the precipitation of diabetes in the predisposed may be related to *hyperfunctioning of endocrine glands* other than the pancreas, notably the *pituitary*. It is well known that glycosuria and diabetes are common in acromegaly, that their incidence in hyperthyroidism is greater than in the population at large, and that they may accompany tumors of the adrenal cortex. One thinks of a possible pituitary background for the overweight so common prior to the onset of diabetes in adult patients and for the overheight seen in children prior to onset. Furthermore

According to the last named theory all fatty acid chains both odd and *even numbered are oxidized at each alternate carbon atom* Splitting then takes place of each keto group to form molecules of acetic acid except where a fragment made up of three carbon atoms forms propionic acid *Ketone acids are then formed by the condensation of two molecules* of acetic acid[14] The ketone acids are acetoacetic (diacetic) acid and beta hydroxybutyric acid acetone the third ketone body is formed from acetoacetic acid

The Formation and Breakdown of Glycogen

Following the absorption of the monosaccharides glucose fructose and galactose from the intestinal tract after the digestion of food the sugar which is not burned directly is stored as glycogen in the liver *muscles and skin The reaction* Glucose ⇄ Glycogen *is a reversible* one glycogen stores are not static but are constantly changing varying with the body s needs

In *recent years a much better idea of the metabolic pathway* traveled by glucose has been gained through the efforts of many investigators Extremely fruitful has been the work of chemists interested in enzymatic processes because it is becoming increasingly apparent that through such means most metabolic transformations are made Metabolic processes then are (1) usually reversible (2) enzymatic in nature and (3) many of them involve the transfer of energy rich phosphate groups These points are illustrated in Figure 1 which shows the most widely accepted view of the formation and breakdown of glycogen Much of the work on enzymes has been done by Cori and his associates[18] In 1939 Cori demonstrated that a glycogen like substance *could be formed in the test tube by the use of glucose 1 phosphate* and the enzyme phosphorylase More recently from Cori s laboratory has come the report that whereas the reaction just mentioned takes place in the absence of insulin definite influence is exerted by insulin in the hexokinase reaction whereby glucose in the presence of adenosine triphosphate is transformed to glucose 6 phosphate and thereby admitted to the metabolic system and endowed with the property of metabolic activity Cori has stated that the hexokinase reaction is opposed either in the test tube or in the *living animal* by extracts of the anterior pituitary and furthermore that the presence of insulin tends

Supporters of the underutilization theory base their belief in part on two considerations (1) The supposedly constant urinary glucose nitrogen (G:N or D:N) ratio during fasting or during maintenance on a diet made up exclusively of protein after exhaustion of glycogen stores The glucose nitrogen ratio in the severest diabetes in man is 3.65:1 and in depancreatized dogs 2.8:1 Actually there is a wide variation in these findings, and many workers[13] regard them as of questionable significance (2) The failure of the respiratory quotient to rise when carbohydrate is fed to a diabetic animal However, Soskin and Levine[13] believe that this does not necessarily indicate an inability to oxidize carbohydrate and remind us that the respiratory quotient must be regarded as the composite total effect of various metabolic processes and not as the index of a single event

No final conclusion is possible at the present time regarding this controversy On the basis of available evidence it is reasonable to assume that there exist both overproduction of glucose and also lessened effectiveness in its oxidation in the tissues As the result of this normal utilization does not take place and proper storage as glycogen in the liver muscles and skin does not occur

Formation of Ketone Bodies

Under normal conditions fat is broken down to ketone bodies in the liver and these are oxidized directly by the tissues as a source of energy In the normal man or animal carbohydrate is used in preference to protein and fat but when carbohydrate stores are exhausted or cannot be used properly as in the uncontrolled diabetic recourse is had to fat to a greater extent As a consequence more ketone bodies are formed than the tissues can utilize and these accumulate in the blood and body tissues generally and are excreted in the urine When this situation prevails acidosis (ketosis) is said to be present The above statement of the situation represents a departure from views held formerly but is in keeping with recent observations and more nearly explains the observed facts Ideas have changed likewise as to the chemical steps by which ketone bodies are formed from fat The Knoop theory of successive beta oxidation' is now held by most workers to be unsatisfactory The theories most widely accepted are Hurtley's multiple alternate oxidation theory or the hypothesis advanced by MacKay and associates of beta oxidation acetic acid condensation

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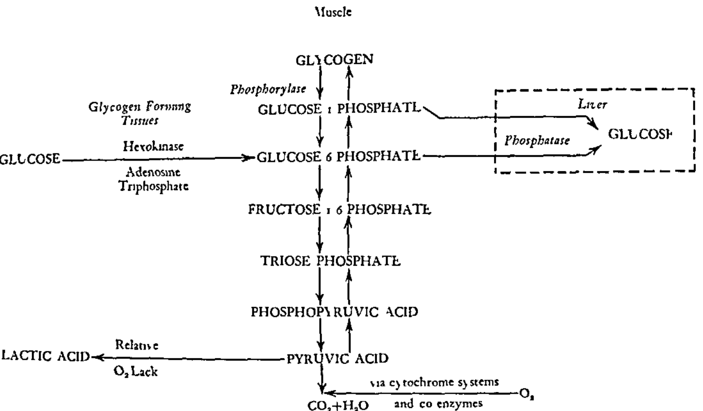


Figure 1 —Formation and breakdown of glycogen and oxidation of carbohydrate (from Best and Taylor[13])

to release the reaction from this inhibition Although adrenal cortical extracts exert no effect on the hexokinase reaction alone they greatly intensify the inhibitory effect of added or previously injected anterior pituitary extracts It is noteworthy that when insulin is reduced by cysteine it is no longer capable of antagonizing the inhibitory effect of anterior pituitary extract on hexokinase activity This is of particular interest because insulin is a disulfide (S S) protein and the activities of various enzymes concerned in carbohydrate metabolism are known to depend on their SH or S S groups It is possible that both insulin and anterior pituitary extract exert their action by affecting the sulfhydryl balance of hexokinase *It seems probable from the results just summarized that one of the main sites of action of insulin is at the hexokinase reaction* Whether this is the only site is open to question and some believe that insulin favors the breakdown of glucose to 3 carbon fragments which later are oxidized to carbon dioxide and water or are used in the formation of fatty acids Final judgment awaits further work

While *Cori s findings regarding the influence of insulin on the hexokinase reaction are consistent with most of the known facts* other workers have had difficulty in confirming his results so that the situation still is not clear Furthermore there are certain points of considerable importance which remain unexplained Thus although insulin opposes the action of anterior pituitary extract it has no direct effect on the hexokinase reaction in the absence of pituitary extract Yet in the living animal when the pituitary gland is removed marked hypoglycemia ensues which may be fatal unless *food or glucose are administered or anterior pituitary extract given* Various *theories have been proposed* to explain this discrepancy but none is entirely satisfactory

Metabolism of Glucose

As pointed out by Stetten[1] from whose article Figure has been taken once glucose has been phosphorylated and thereby admitted to the metabolic system various pathways are open to it Glucose 6 phosphate may be split in the liver through the action of *the enzyme phosphatase to reform glucose since phosphatase is absent from muscle liver glycogen is the only source of blood sugar and the blood sugar of the liverless animal quickly falls to zero* Glucose 6 phosphate through

the Embden-Meyerhof cycle may be broken down to pyruvate, lactate and other 3-carbon fragments As shown in Figure ., a part of these 3-carbon compounds enter into the formation of fatty acids (lipogenesis) and a part is broken down through the Krebs tricarboxylic acid cycle to carbon dioxide and water Stetten and Boxer[1] have reported that in the well nourished rat only about 3 per cent of

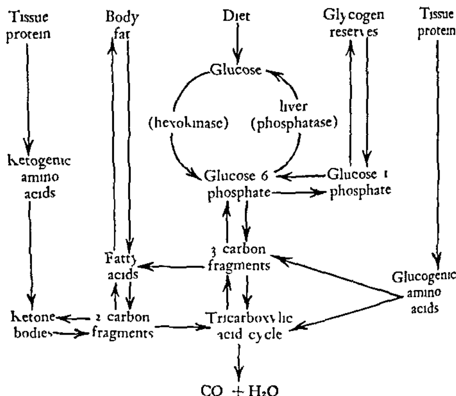


Figure 2 — The fate of glucose in the body (from Stetten D Jr[17])

the glucose ingested is converted each day to glycogen while about 30 per cent ten times as much is used in the formation of fatty acids

Figure . illustrates another important concept that of the interrelationship of carbohydrate protein and fat in the body economy Their degradation products contribute in part to a common metabolic pool' in which new combinations may take place Thus the metabolic processes concerned with carbohydrate protein and fat take place not in separate distinct compartments but rather in an integrated fashion

Influence of Other Glands of Internal Secretion

Although to the pancreas must be assigned the major role in carbohydrate metabolism other glands of internal secretion have a profound effect Some workers have gone so far as to suggest that extra insular influences are paramount The glands most concerned are the pituitary and the adrenal glands although the thyroid and the gonads undoubtedly exert some effect

Much of the original work regarding the relationship of the *anterior pituitary* on carbohydrate metabolism has been carried out by Houssay and collaborators[19] At first with large South American toads and later with dogs they showed conclusively that hypophysectomy greatly ameliorates the diabetic condition of a previously depancreatized animal Hyperglycemia glycosuria and ketonuria are much less in the doubly-operated animals than in those subjected to pancreatectomy alone Hypoglycemia is common particularly if the animals are fasted and hypersensitivity to insulin is the rule The injection of anterior pituitary extract causes a return of the diabetic state The Houssay animals demonstrate incidentally that total lack of the pancreas and insulin is not incompatible with existence since the animals live for certain periods though they are far from well It would appear that the tissues probably through enzyme activity are capable of carrying out to a limited extent metabolic activities which are greatly enhanced or modified by insulin

In addition to the above Houssay and associates H M Evans[0] and others showed that the injection of crude anterior pituitary extract into normal dogs causes hyperglycemia and glycosuria It remained for Young[1] however to demonstrate in 1937 that if the daily intraperitoneal injection of such extracts is continued for a period of two to four weeks in adequate dosage the resulting diabetes is permanent and persists despite cessation of the injections Histological examination of the pancreas of such animals shows initially degranulation and hydropic degeneration in the beta cells of the islands of Langerhans In animals made permanently diabetic widespread irreversible destruction of islet tissue is produced It seems logical to suppose that the diabetes results because of exhaustion of the islets due to the persistent long continued hyperglycemia induced by the injections of anterior pituitary extract That the hyperglycemia may be the responsible factor is suggested by the fact that in the early stages of the development of

pituitary diabetes the production of permanent diabetes may be prevented by means of three agents, insulin a low calorie diet and phlorhizin all of which tend to diminish or abolish hyperglycemia

The adrenocorticotrophic hormone of the pituitary (ACTH) has diabetogenic properties causing glycosuria and lowered glucose tolerance in normal persons[3] and an increased insulin requirement in known diabetes However, pure growth hormone has been shown in appropriate animals to be even more diabetogenic

It is well known that epinephrine the secretion of the *adrenal medulla* tends to raise the blood sugar by increasing the breakdown of glycogen in the liver It is likely, therefore, that epinephrine plays an important part in the maintenance of homeostasis as regards blood sugar Its continued administration, however, does not cause diabetes nor does the destruction of both adrenal medullae ameliorate the diabetes of a depancreatized animal However, when both adrenal glands are removed completely, such amelioration takes place[3], thus indicating the important role of the *adrenal cortex* Furthermore the administration of adrenal cortical extract to animals when the adrenal glands and the pancreas have been removed, increases the severity of the diabetes

The production of diabetes in rats has been reported following the giving of adrenal cortical steroids to animals previously subjected to partial removal of the pancreas[4] The administration of cortisone to human patients with diabetes usually causes a well marked increase in the insulin requirement

Although the influence of the *thyroid gland* upon carbohydrate metabolism is definite it is not nearly as direct or important as that of the anterior pituitary or the adrenal cortex The giving of thyroid to normal animals does not produce diabetes although it is true that Houssay succeeded in producing metathyroid" diabetes by the administration of thyroid extract to dogs handicapped by earlier partial pancreatectomy

The influence of the *gonads* and gonadotropic substances on carbohydrate metabolism both of man and experimental animals has been the subject of many investigations However no direct or striking relationships have been brought out except perhaps the clinical fact that the onset of diabetes often comes in women at or near the menopause There is much disagreement as to the effect of the administration of estrogens on the diabetic condition of such women

Lipotropic Substances

Lipotropic substances are those which prevent or remove an accumulation of excess fat in the liver. Three such factors are recognized[4], (1) choline and related compounds including methionine from which the body can synthesize choline ( ) lipocaic and (3) inositol

Shortly after the discovery of insulin it was found that in order to keep totally depancreatized animals alive and in good condition it was necessary to give them not only insulin and a diet consisting of lean meat and sugar but also to provide rations of raw pancreas. Later it was found that *lecithin* was the substance in raw pancreas which was responsible for the beneficial results and still later it was noted that *choline* and its chemical relative *betaine* likewise were effective. Prior to the introduction of protamine insulin in 1937 it was not uncommon to find marked hepatomegaly in children with severe diabetes. Since it was assumed and probably rightly so that the livers were filled with fat and that the fat metabolism was disturbed a clinical trial of betaine was made. The results were disappointing but when such children were transferred to protamine insulin and later to protamine zinc insulin hepatomegaly and the accompanying signs and symptoms cleared up almost uniformly. This indicated that in the human diabetic the disorder was due chiefly to inadequately controlled diabetes rather than to lack of choline. Since choline is a most ubiquitous substance and is present in many foodstuffs most dietaries provide ample amounts of it

Some years ago Dragstedt and associates[5] prepared fat free alcoholic extracts of the pancreas to which they ascribed fat metabolizing properties and which they named *lipocaic*. They reported that when this substance was given orally to depancreatized dogs maintained with insulin abnormal accumulation of fat in the liver was prevented and survival time of the animals prolonged. Although Dragstedt has maintained that lipocaic is not identical with choline the status of lipocaic cannot be regarded as settled

Dragstedt and associates reported that *inositol* exerted some lipotropic effect in depancreatized dogs. However its exact role awaits clarification. McHenry and Patterson[6] believe that the lipotropic action of inositol like that of choline is due to its effect in the formation of phospholipids the form in which fats are transported in the body

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though some basis for this is afforded by the close chemical relationship of alloxan to uric acid to date no positive evidence has been brought forth to indicate any etiological connection However of interest is a preliminary report by Griffiths[37] that in rabbits fed diets low in cystine and methionine with resulting low blood levels of glutathione the injection of uric acid results in hyperglycemia and glycosuria Collins Williams and Bailey[11] were unable for the most part to confirm these observations It is possible that the discrepancy is related to the type of rabbits used Possibly related to this report are the findings of Conn Louis and Wheeler[9] that the daily intramuscular administration of purified adrenocorticotropic hormone produces in man temporary glycosuria and lowered glucose tolerance There was a close correlation between loss of carbohydrate tolerance and increased excretion of uric acid in the urine In one subject in whom determinations of blood glutathione were carried out the lowest levels were obtained during the period that adrenocorticotropic hormone was administered Conn and associates suggest that these changes seen during the giving of adrenocorticotropic hormone may possibly diminish enzymatic production or release of pancreatic insulin

The second question of importance clinically is concerned with the possible use of alloxan in the treatment of hyperinsulinism in human patients[36] Experience indicates that alloxan is a dangerous substance which may produce liver necrosis and fatal toxic reactions at present its use in humans is to be condemned Although it may destroy normal islet cells islet cell adenomas appear resistant to its action [7]

An excellent summary of the literature regarding alloxan diabetes may be found in the article by Lukens[35]

Diabetes following Glucose Injections—Dohan and Lukens[39] have shown that the intraperitoneal injection of 50 to 140 c c of o per cent glucose solution every 8 hours for . to 4 weeks may cause diabetes in not only partially depancreatized but also normal cats The diabetic condition remains permanent after discontinuance of the injections Histological examination of the pancreas shows hydropic degeneration of the beta cells of the islets

Of the four types of experimental diabetes at least two pituitary diabetes and diabetes following glucose injection appear to depend upon long continued hyperglycemia for the critical changes in islet tissue If the hyperglycemia expected following injection of anterior pituitary extract is prevented by the concomitant giving of insulin or phloridzin diabetes does not result It would appear then that

Production of Diabetes in Animals

Diabetes may be produced in suitable normal animals by the following methods (1) surgical removal of at least nine tenths of the pancreas (2) administration of anterior pituitary or adrenal cortical extracts (3) injection of alloxan and (4) repeated parenteral injection of glucose The first two methods have been discussed already, the other two deserve mention because of their possible application to human diabetes

Alloxan Diabetes—Although in 1899 Wiener[3] noted that the administration of alloxan to rabbits caused convulsions and death and in 1937 Jacobs[30] demonstrated that the convulsions were hypoglycemic no great interest was aroused until in 1943 Dunn, Sheehan and McLetchie[31] showed histologically that in such rabbits there was a selective necrosis of the islets of Langerhans of the pancreas Bailey and Bailey[3] reasoned that, if animals given alloxan could be kept from dying during the critical period of hypoglycemia they probably would develop permanent diabetes This proved to be so and at about the same time Goldner and Gomori and associates[33] showed that the same result could be secured with dogs Since then permanent diabetes has been produced in rats monkeys and other animals by means of alloxan and certain chemical relatives of alloxan The procedure has become recognized as a quick and relatively easy method for the preparation of diabetic animals

Experience has shown that clinically alloxan diabetes resembles diabetes occurring spontaneously in man identical symptoms may occur, the condition may be modified by treatment with a restricted diet and/or insulin and complications such as acidosis and cataracts may occur On the other hand histological study of the pancreas shows no such close resemblance between alloxan and human diabetes In alloxan diabetes acute necrosis of the islet cells is characteristic, such is exceedingly rare in human diabetes It is true that in diabetes produced slowly by repeated small doses of alloxan hydropic degeneration of islet cells may be noted at certain stages and that such histological changes are seen at times albeit infrequently, in the pancreases of human diabetics However as far as pathology is concerned perhaps one should not be surprised to find that acute changes produced by a chemical do not resemble chronic changes seen after years of diabetes

The preceding discussion is pertinent to the question as to whether alloxan could bear any relation to the origin of human diabetes Al

procedures they were aided by Collip Scott and others Insulin was prepared first in crystalline form by Abel and co workers in 19 6

Properties of Insulin[13]

Crystalline insulin gives all the reactions of a typical protein It is precipitated by the usual protein precipitants and is denatured by strong acid or by boiling It dissolves readily in dilute acid dilute alkali and 90 per cent phenol It is somewhat soluble in 80 per cent alcohol and insoluble in water free organic solvents The melting point is 233°C the molecular weight is about 35 000 (approximately that of egg albumin) and the iso-electric point is at pH 5 2 It is optically active and levorotatory Approximately 95 per cent of the constituents of the insulin molecule have been identified The amino-acids cystine tyrosine glutamic acid leucine arginine histidine lysine proline and phenylalanine have been isolated and identified All of the sulphur, 3 . per cent is present as the disulphide (S S) linkage There has long been recognized a definite relationship between physiological activity and the labile sulphur If the protein structure of insulin is affected by hydrolysis through chemical or enzymic means the physiological activity is lost

Insulin is the product of the beta cells of the islands of Langerhans of the pancreas Conclusive proof of this is afforded in the fact that insulin can be extracted from metastatic nodules arising from islet cell carcinomata in cases of hyperinsulinism The secretion of the beta cells leaves the gland by way of the blood stream and passes first to the liver Nerve impulses affecting the islet cells are conducted by the vagus A rich plexus of myelinated nerve fibers surrounds each islet and both myelinated and non myelinated fibers are said to invade the islet tissue itself Although certain studies with pancreatic grafts suggest that the islet cells can be stimulated by humoral influences alone it is probable that the secretion of insulin is under the control of the vagus center which depends for its stimulation on the height of the blood sugar

Scott and Fisher[14] reported that the insulin content of pancreases of 14 normal persons averaged 1 7 units of insulin per gram whereas that of the pancreases of 18 diabetic persons averaged less than 0 4 units per gram Haist Best and associates[5] found in rats that fasting fat feeding and the giving of insulin caused a reduction in the insulin content of

diabetes following pituitary extract or glucose is due to overwork and final exhaustion of the islet cells due to long-continued hyperglycemia[38] Further application of this principle is seen in animals subjected to subtotal pancreatectomy but with enough pancreas remaining to prevent diabetes If such handicapped animals are overfed permanent diabetes may result again presumably due to overwork and exhaustion of the islet cells

Such observations as the above indicate that persistent hyperglycemia in the diabetic cannot be regarded lightly even though acidosis is not present They give strong support to the teaching that the careful treatment of diabetes pays The writer believes that the goal in treatment should be to restore by means of careful treatment with diet and insulin physiological conditions in so far as practicable He believes that only in this way can the complications both acute and chronic be prevented

Insulin

Three decades before the discovery of insulin by Banting and Best in 1921 its production by cells of the islands of Langerhans of the pancreas had been suggested by Laguesse[10] During these thirty years many workers tried with varying degrees of success to prepare from the pancreas an extract which would consistently lower the blood sugar Some almost succeeded and came closer to the goal than they themselves realized Perhaps the most successful was Zuelzer[11] who even treated several diabetic patients by injection of extracts but his work was discontinued because of untoward toxic effects Banting and Best carried out their work during the summer of 1921 and their results were reported publicly and published in the fall of that year[1] The first injection of their extract into a human diabetic patient took place in the Toronto General Hospital on January 11 1922 Insulin was introduced into large clinics in the late summer of 1922 and by 1923 was available generally With these early patients as with the many thousands treated subsequently remarkable benefit was seen immediately

The method developed by Banting and Best for the preparation of insulin consisted of an extraction of the pancreas with acid alcohol and subsequent concentration and purification In the development of their

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Crystalline insulin gives all the reactions of a typical protein It is precipitated by the usual protein precipitants and is denatured by strong acid or by boiling It dissolves readily in dilute acid dilute alkali and 90 per cent phenol It is somewhat soluble in 80 per cent alcohol and insoluble in water free organic solvents The melting point is 233°C the molecular weight is about 35 000 (approximately that of egg albumin) and the iso-electric point is at pH 5 2 It is optically active and levorotatory Approximately 95 per cent of the constituents of the insulin molecule have been identified The amino-acids cystine tyrosine glutamic acid leucine arginine histidine lysine proline and phenylalanine have been isolated and identified All of the sulphur 3 per cent is present as the disulphide (S S) linkage There has long been recognized a definite relationship between physiological activity and the labile sulphur If the protein structure of insulin is affected by hydrolysis through chemical or enzymic means the physiological activity is lost

Insulin is the product of the beta cells of the islands of Langerhans of the pancreas Conclusive proof of this is afforded in the fact that insulin can be extracted from metastatic nodules arising from islet cell carcinomata in cases of hyperinsulinism The secretion of the beta cells leaves the gland by way of the blood stream and passes first to the liver Nerve impulses affecting the islet cells are conducted by the vagus A rich plexus of myelinated nerve fibers surrounds each islet and both myelinated and non myelinated fibers are said to invade the islet tissue itself Although certain studies with pancreatic grafts suggest that the islet cells can be stimulated by humoral influences alone it is probable that the secretion of insulin is under the control of the vagus center which depends for its stimulation on the height of the blood sugar

Scott and Fisher[14] reported that the insulin content of pancreases of 14 normal persons averaged 1 7 units of insulin per gram whereas that of the pancreases of 18 diabetic persons averaged less than 0.4 units per gram Haist Best and associates found in rats that fasting fat feeding and the giving of insulin caused a reduction in the insulin content of

the pancreas They concluded that the effects observed were due to resting of the islets

Insulin Requirement of Man

There has been much speculation as to the number of units of insulin required by the average normal human being and estimates have varied widely from 50 to 200 or 300 units daily Within the past few years it has been possible to obtain a direct answer to this problem In those patients in whom total removal of the pancreas has been carried out because of carcinoma or other reasons the insulin requirement has been found to be uniformly low 30 to 50 units daily[17] Surprisingly the insulin requirement of a partially depancreatized dog with diabetes falls with removal of the last remnants of pancreatic tissue It has been suggested that this phenomenon is due to a hyperglycemic principle produced by the alpha cells of the islands of Langerhans

Methods of Administration

Insulin is a protein and as such is destroyed by digestive juices thereby losing potency The only practical effective means of administering insulin at the present time is by parenteral injection Many attempts have been made to give insulin in such a form as to protect it from the destructive influence of digestive juices but these have not been strikingly successful In the most promising of studies some effect upon the blood sugar is obtained but such effects are slight and variable and require many times the number of units to secure a given effect as would be required by subcutaneous administration[47]

Sensitivity to Insulin and 'Insulin Resistance"

It is a common clinical finding that diabetic patients vary greatly in their sensitiveness to insulin There are many exceptions but in general juvenile adolescent and young adult patients with severe diabetes are most apt to respond markedly to an injection of insulin whereas older individuals by and large are relatively insensitive It is fair to state that no patient has been shown to be totally resistant to

insulin there are rare cases in which from 500 to [illegible] 000 or more units a day have been needed[illegible] but invariably if the dosage is sufficiently great an effect upon the blood sugar has been secured. Sensitivity to insulin varies greatly among animals; birds are less sensitive than mammals. For a comprehensive discussion of the subject of insulin resistance see the article by Smelo[115].

Various tests have been devised in an attempt to determine the degree of sensitivity to insulin of human patients as an aid in classification and treatment. Such a test is one proposed by Radoslav and modified by workers in Falta's clinic[9] in which the effect of a definite amount of insulin on the capillary and venous blood sugar of a fasting subject is determined over a period of 4 to 5 hours. Another type of test is that used by Himsworth[1] in which a fasting subject is given glucose by mouth and insulin by vein in doses calculated per kilogram of body weight. Determinations of the capillary blood sugar are made at frequent intervals for the following hour and a half. In insulin-sensitive persons the blood sugar rise which ordinarily would follow the giving of glucose is wholly or partly prevented by the insulin, whereas in insensitive subjects the injection of insulin has little or no effect on the blood sugar rise.

It is true that by tests such as those just mentioned persons both diabetic and non-diabetic may be classified as to their sensitivity to insulin. From a practical standpoint, however, it has been the experience of most physicians that the results of such tests cannot be correlated with clinical responses to a degree sufficient to be of help in the classification and treatment of patients. Most clinicians prefer to gain an impression of the degree of sensitivity to insulin through its day by day use.

Pathology

The first case of diabetes recognized during life in which a lesion of the pancreas was noted at postmortem examination was described by Thomas Cawley in 1788. In this patient the pancreas was found to be filled with calculi. The relation of the pancreas to diabetes was placed on a firm basis by the discovery in 1889 by von Mering and Minkowski that diabetes follows the complete removal of the pancreas in the dog, rabbit and pigeon. Confirmatory evidence of the outstanding role of the pancreas was furnished by Banting and Best's success in extracting from the islet tissue of the pancreas a substance which would lower

the blood sugar and transform diabetic men and animals into essentially normal individuals.

Findings in Pancreas

With the above facts in mind one might suppose that the examination of the pancreas of diabetics at postmortem would show characteristic and striking changes. Certainly this is true in those animals made diabetic by the production of long sustained hyperglycemia following the injection of anterior pituitary extract or glucose. In such animals the early lesions are degranulation and hydropic degeneration of the beta cells. These changes are followed by apparent death of the beta cells presumably due to excessive stimulation and overwork. The final result is that of atrophy of the islet tissue with ingrowth of fibrous tissue and scarring. Likewise in the diabetes caused by alloxan unmistakable and marked destruction of the islet cells takes place. In the human diabetic, however the pancreas usually is grossly normal and on microscopic examination no characteristic appearance is consistently seen. It must be emphasized however, that in most diabetics the histological appearance is not entirely normal as one is led to believe by the writings of many.

Warren[3] has described the following four types of changes seen in the pancreas of diabetics, (1) hydropic degeneration, (2) hyalinization, (3) fibrosis and (4) lymphocytic infiltration.

Hydropic degeneration is a process in which specific granules in the beta cells disappear and are replaced by vacuoles which grow and coalesce until the cytoplasm of the cells seems to be replaced by a watery fluid. This is an undoubted early lesion in experimental diabetes and is reversible in the early stages of its development. There is much evidence to indicate that it arises by overwork of the beta cells. However in human diabetics its importance is difficult to assay since it can be simulated very closely by postmortem changes. In Warren's 484 autopsies unquestioned hydropic degeneration occurred only [illegible]2 times.

Hyalinization of the islands of Langerhans was found by Warren to a varying degree in [illegible]00 of his 484 cases and is generally considered to be the most typical pancreatic lesion in diabetes. It is most common in older persons and in those with mild diabetes. In Warren's material 45 per cent of patients over 40 years of age showed hyaline degeneration as contrasted with 6 per cent of cases up to and including 40 years of age.

Next to hyalinization *fibrosis* of the pancreatic islets is the change most commonly noted in diabetes having been present in 129 of Warren's 484 cases However in 73 of the 129 cases the fibrosis or sclerosis was only slight Fibrosis like hyalinization tends to occur in older individuals and the two processes may coexist However, of the lesions found in young patients fibrosis is one of the most common

In 9 or 2 per cent of Warren's cases the histological change was that of *lymphocytic infiltration* in and about the islets This type of change is particularly apt to be found in young individuals 7 of Warren's 9 patients showing this lesion were under 30 years of age Warren associates this lesion with severe diabetes and noted it chiefly in those patients with relatively short duration of the disease

As stated above it is not uncommon to find the pancreas histologically *normal in patients with undoubted diabetes* In Warren's series of 484 pancreases 127 or more than one fourth showed islands which appeared normal histologically The probability cannot be denied however that the islet tissue although appearing normal anatomically *may be functionally inadequate* It is also conceivable that the pancreas in diabetes might secrete insulin adequate under ordinary conditions in both quantity and quality and yet the effectiveness be impaired by overwhelming influences arising outside the pancreas

Findings Outside Pancreas

Although the pancreas holds the center of the stage in diabetes it is imperative to consider possible changes in other organs and tissues In most instances however in uncomplicated and particularly in early diabetes postmortem examination may yield general findings within normal limits Although one rightly suspects the pituitary and adrenal glands as being at fault in the pathogenesis of at least certain cases of diabetes only in rare instances does one find at autopsy any abnormality in these glands The same is true of the thyroid and gonads In the older literature there was frequent reference to an enlarged and fatty liver in diabetes but in Warren's series the incidence of such was not striking in comparison with non diabetic controls Of especial interest in the histological examination of the liver in uncontrolled diabetes is the relative lack of glycogen in the usual site namely in the cytoplasm of the cells and its presence to a greater or less degree in the nuclei The bringing of diabetes under control with the use of insulin

the blood sugar and transform diabetic men and animals into essentially normal individuals

Findings in Pancreas

With the above facts in mind one might suppose that the examination of the pancreas of diabetics at postmortem would show characteristic and striking changes Certainly this is true in those animals made diabetic by the production of long sustained hyperglycemia following the injection of anterior pituitary extract or glucose In such animals the early lesions are degranulation and hydropic degeneration of the beta cells These changes are followed by apparent death of the beta cells presumably due to excessive stimulation and overwork The final result is that of atrophy of the islet tissue with ingrowth of fibrous tissue and scarring Likewise in the diabetes caused by alloxan unmistakable and marked destruction of the islet cells takes place In the human diabetic however the pancreas usually is grossly normal and on microscopic examination no characteristic appearance is consistently seen It must be emphasized however that in most diabetics the histological appearance is not entirely normal as one is led to believe by the writings of many

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Hyalinization of the islands of Langerhans was found by Warren to a varying degree in 200 of his 484 cases and is generally considered to be the most typical pancreatic lesion in diabetes It is most common in older persons and in those with mild diabetes In Warren's material 45 per cent of patients over 40 years of age showed hyaline degeneration as contrasted with 6 per cent of cases up to and including 40 years of age

from 1944 to 1949 just referred to 1 596 or 69 4 per cent were due to arteriosclerotic manifestations in the heart brain kidneys or extremities with frequency in the order named Arteriosclerosis must be regarded as one of the degenerative complications of diabetes and by far the most important At the present time the exact mode of production of arteriosclerosis by diabetes is not well understood However one thing seems clear namely that diabetes causes arteriosclerosis and not the reverse as has been maintained often in the past There is ample evidence to indicate that arteriosclerosis is a sequel and not a cause of diabetes Data to support this can be assembled among older age groups but it is among youthful diabetic patients that the facts stand out so clear as to defy contradiction In patients with onset of diabetes at the age of 15 years and under one can now study the course of the disease in relatively pure form over many years of time It is not until usually 10 or more likely 15 or even 20 years of diabetes that x ray evidence of calcification in the arteries can be seen in the aorta pelvic vessels and arteries supplying the legs Arteriosclerosis of advanced degree can be seen in some of these young people who although their diabetes is of 20 years duration are still under the age of 35 years As will be brought out *in some detail later in the* section on Treatment of Diabetes in Childhood fully 80 per cent of children with diabetes over 20 years duration and onset under the age of 15 show some degree of arteriosclerosis'

The chief characteristic of arteriosclerosis in the diabetic is the occurrence of intimal sclerosis (atheromatosis) in muscular arteries This type of arteriosclerosis in the non diabetic usually is confined to the elastic arteries such as the aorta the iliac and the carotid arteries In addition in the diabetic intimal sclerosis in the muscular arteries *such as those supplying the legs is often accompanied by or super* imposed upon medial calcification (Monckeberg s sclerosis) Arterial occlusion in peripheral vessels producing the typical diabetic gangrene is often a gradual process characterized by a progressive encroachment on the lumen of the vessel by thickening of the intima which may show large deposits of lipoid material Fortunately because of the gradual nature of this process there is often time for collateral circulation to develop

The cause of arteriosclerosis and its unusually high incidence in *diabetes is not clear despite a great deal of investigative work on the* subject At the present time the most that can be said is that arterio-sclerosis appears to be related to the disturbed metabolism of made

results in restoration of glycogen stores in the cytoplasm and its disappearance from the nuclei Stored glycogen is most marked in those cells in the periportal region

Warren states that in the pre-insulin days practically every case of active diabetes treated or untreated, showed glycogenic infiltration of *the epithelium of Henle's loops of the kidney* It is not an essential lesion of diabetes, however as shown by its absence in many insulin treated cases Since it is found in glycosuria of all types including that caused by phloridzin, it would appear to be related more to the presence of sugar in the urine than to any feature characteristic of diabetes

In recent years another type of kidney finding has been described which is of great importance and thought by some to be characteristic of diabetes Reference is made to the so-called intercapillary glomerulosclerosis described first by Kimmelstiel and Wilson[3] The striking pathological changes are hyalinization to a greater or less degree of many glomeruli Hyaline masses appear to lie between the capillaries of the glomerular tufts Arteriosclerosis of high degree is seen not only in the arterioles within the glomeruli but also in the afferent vessels Patients showing this lesion at postmortem examination often have been noted during life to have albuminuria hypertension and retinopathy together with a nephrotic syndrome, hypoproteinemia and reversal of the albumin globulin ratio[4] However, as Wilson Root and Marble have pointed out (paper to be published), intercapillary glomerulosclerosis is only one feature of the mixed nephropathy often encountered in patients with diabetes of long duration

Cardiovascular System—In the pre-insulin days diabetic coma was the chief cause of death among diabetic patients young and old and in children was the almost inevitable culmination of a diabetic life after not more than two years of the disease In the experience of Joslin and associates[8] of 326 deaths from 1898 to 1914, 208 or 63.8 per cent were in coma Even in the period from 1914 to 1922, 41.5 per cent of 836 deaths were in coma With the discovery and use of insulin deaths from acidosis fell dramatically so that in the last series tabulated of [illegible]99 death from 1944 to 1949 only 1.9 per cent were in diabetic coma With the conquest of coma and the lengthening life of diabetics, there has become apparent the marked influence of diabetes on the vascular system over a period of 10 15 or 20 years Further reference to this will be made later in the discussion but it is appropriate now to call attention to the fact that arteriosclerosis has changed place with diabetic coma as the chief cause of death Thus of the [illegible]99 deaths

TABLE II — THE CAUSES OF DEATH OF 10,673 DIABETICS 1898-1949
(Experience of Elliott P. Joslin, M.D. and Associates)

Cause of Death	1898 to May 31 1914 Deaths	Per Cent of all cases	June 1 1914 to Aug 6 19 Deaths	Per Cent of all cases	Aug 7 19 2 to Dec 31 19 6 Deaths	Per Cent of all cases	Jan 1 1937 to Dec 31 1943 Deaths	Per Cent of all cases	Jan 1 1944 to April , 1949 Deaths	Per Cent of all cases
All causes	326	100.0	836	100.0	4061	100.0	3151	100.0	2299	100.0
1 Diabetic coma	08	63.8	347	41.5	340	8.4	98	3.1	43	1.9
2 Cardio renal vascular	57	17.5	06	24.6	2200	54	2047	65.0	1612	0 1
Arteriosclerotic	5	17.5	203	4.3	2184	53.8	2035	64.6	1596	69.4
a Cardiac	20	6.1	83	9.9	1206	29.7	1287	40.8	1054	45.8
b Nephritic	11	3.4	32	3.8	190	4.7	140	4.4	161	7.0
c Apoplexy	9	2.8	41	4.9	381	9.4	368	11.7	269	11.7
d Gangrene	12	3.7	35	4.2	323	8.0	160	5.1	71	3.1
e Site unassigned	5	1.5	12	1.4	84	2.1	80	2.5	41	1.8
Other circulatory and rheumatic heart diseases	0	0.0	3	0.4	16	0.4	12	0.4	16	0.7
3 Infections total	4	7.4	106	12.7	557	13.7	345	10.9	153	(7
Pneumonia and respiratory	14	4.3	64	7.7	281	6.9	187	5.9	93	4.1
Carbuncle	6	1.8	13	1.6	40	1.0	16	0.5	0	0.0
Kidneys acute	0	0.0	1	0.1	36	0.9	29	0.9	18	0.8
Other infections	4	1.3	28	3.3	00	4.9	113	3.6	42	1.8
4 Cancer	5	1.5	32	3.8	353	8.7	2,7	8.8	05	8.9
5 Tuberculosis	16	4.9	41	4.9	163	4.2	8	2.5	48	1
6 Diabetes	8	2.5	56	6.7	1 0	3.0	99	3.1	61	2.7
7 Accidents	0	0.0	7	0.8	84	2.1	57	1.8	44	1.9
8 Inanition	1	0.3	18	2.2	6	0.1	0	0.0	0	0.0
9 Suicides	1	0.3	2	0.2	27	0.7	21	0.7	13	0.6
10 Hypoglycemia due to Insulin	0	0.0	0	0.0	8	0.2	10	0.4	7	0.3
11 Other Diseases	6	1.8	21	2.5	197	4.9	119	3.8	113	4.9

Table prepared by the Statistical Bureau of the Metropolitan Life Insurance Company. Deaths reported to April 27, 1949

quately controlled diabetes. Whether the vascular changes are due to hypercholesteremia, damage from long-continued subclinical acidosis or a combination of factors cannot be regarded as settled. The importance of cholesterol in the pathogenesis of experimental arteriosclerosis in animals is unquestioned, but present evidence is insufficient to warrant direct transference of conclusions from animals to man. Recent work by Gofman and co-workers[119] suggests that the blood level of large lipoprotein molecules (S_f 10-20) may be correlated with atherosclerosis and its complications.

Causes of Death

Over many years of time a systematic follow-up of patients seen by Joslin and associates[5] has been carried out. In this work and more particularly in the statistical handling of data obtained cooperation has been furnished by the Statistical Bureau of the Metropolitan Life Insurance Company. Various studies have been made but for the purpose of showing the trend in diabetes over the past 40 or more years no summary of data is more enlightening than that shown in Table II in which are listed the causes of death of 10 673 diabetics. One notes a steady fall in the mortality from diabetic coma from 1898-1914 to 1944-1949 and a corresponding rise in the percentage of deaths due to arteriosclerosis. The mortality from infections including tuberculosis has fallen. That for cancer has been greater since 1922, probably because the longer life made possible with insulin has brought more persons in the age zone in which malignant disease is common.

Expectation of Life

With constant improvement in methods of treatment has come a steady increase in the life expectancy of the diabetic. As is evident from Table III in 1898-1914 the average patient died at the age of 44.5 years after 4.9 years of diabetes. In the latest group studied (1944-1946) the average age at death was 64.[illegible] years and the average duration of diabetes 14.1 years. At the present time the life expectancy of the average adult diabetic is about ¾ that of the average non-diabetic of the same age.

TABLE II — THE CAUSES OF DEATH OF 10 673 DIABETICS 1898 1949
(Experience of Elliott P Joslin M D and Associates)

Cause of Death	1898 to May 1 1914 Deaths	Per Cent of all cases	June 1 1914 to Aug 6 1922 Deaths	Per Cent of all cases	Aug 7 1922 to Dec 31 1936 Deaths	Per Cent of all cases	Jan 1 1937 to Dec 31 1943 Deaths	Per Cent of all cases	Jan 1 1944 to April 7 1949 Deaths	Per Cent of all cases
All causes	3 6	100 0	836	100.0	4061	100 0	3151	100.0	2 99	100.0
1 Diabetic coma	208	63 8	347	41 5	340	8.4	98	3 1	43	1 9
Cardio renal vascular	57	17 5	106	4 6	2 00	54 2	2 47	65.0	1612	0 1
Arteriosclerotic	57	17 5	203	24 3	2184	53 8	2035	64 6	1596	69.4
a Cardiac	0	6 1	83	9 9	1 06	29 7	1 67	40 8	1054	45 8
b Nephritic	11	3.4	32	3 8	190	4 7	140	4.4	161	.0
c Apoplexy	9	8	41	4 9	381	9.4	368	11 7	269	11 7
d Gangrene	1	3 7	35	4 2	323	8 0	160	5 1	71	3 1
e Site unassigned	5	1 5	12	1.4	84	2 1	80	5	41	1 8
Other circulatory and rheumatic heart diseases	0	0.0	3	0.4	16	0.4	12	0.4	16	0 7
3 Infections total	4	7.4	106	12 7	557	13 7	345	10 9	153	6 7
Pneumonia and respiratory	14	4 3	64	7 7	81	6 9	197	5 9	93	4 1
Carbuncle	6	1 8	13	1 6	40	1.0	16	0 5	0	0 0
Kidneys acute	0	0 0	1	0 1	36	0 7	9	0 9	18	0 8
Other infections	4	1 3	28	3 3	200	4 9	113	3 6	4	1 9
4 Cancer	5	1 5	32	3 8	353	8 7	2/7	8 8	95	8.9
5 Tuberculosis	16	4 9	41	4 9	169	4 2	8	2 5	48	2 1
6 Diabetes	8	5	56	6 7	120	3 0	99	3 1	61	2 7
7 Accidents	0	0 0	7	0 8	84	2 1	57	1 8	44	1 9
8 Inanition	1	0 3	18	2 2	6	0 1	0	0 0	0	0 0
9 Suicides	1	0 3	2	0 2	27	0 7	21	0 7	13	0 6
10 Hypoglycemia due to Insulin	0	0 0	0	0 0	8	0 2	10	0.4	7	0 3
11 Other Diseases	6	1 8	21	2 5	197	4 9	119	3 8	113	4 9

Table prepared by the Statistical Bureau of the Metropolitan Life Insurance Company Deaths reported to April 27 1949

TABLE III

THE CHANGING AVERAGE AGE AT DEATH AND AVERAGE DURATION OF DIABETES 1898 1949*

(Experience of E P Joslin M D and Associates)

Era	No of deaths	Average age at death yrs	Average duration of diabetes yrs
1898 to June 1 1914	326	44.5	4.9
June 1 1914 to Aug 6 19 2	836	46.7	6.1
Aug 7 19 2 to Dec 31 1925	5 8	54.3	7.5
Jan 1 19 6 to Dec 31 19 9	919	60.0	8.4
Jan 1 1930 to Dec 31 1936	2604	62.9	10.4
Jan 1 1937 to Dec 31 1943	3151	64.7	1 5
Jan 1 1944 to April 7 1949	299	64.3	14.4

Adapted from a table prepared by the Statistical Bureau of the Metropolitan Life Insurance Company

The increasing longevity of diabetics is shown in graphic form in Figure 3 prepared by the Statistical Bureau of the Metropolitan Life Insurance Company from data of the George F Baker Clinic The steady increase in life expectancy at the 3 representative ages, 10, 30 and 50 years, is striking

Symptoms and Signs

Symptoms

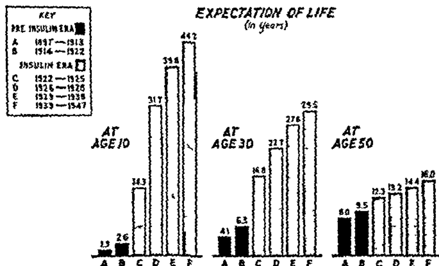
The classical symptoms of diabetes are polyuria, polydipsia, polyphagia and loss of weight and strength To these must be added pruritus, particularly of the external genitals, pruritus vulvae is a common complaint in women with uncontrolled diabetes, and balanitis occurs occasionally in men Of the group of symptoms mentioned, polyphagia is probably the least common, and increased appetite often is not complained of until the patient is put on a restricted diet

In addition to the above symptoms there is a variety of complaints made by diabetic patients when they first present themselves for treatment These include visual disturbances chiefly blurring of vision a tendency to skin infections such as boils and carbuncles and pains down the extremities At times symptoms may be marked Dryness of the mouth and excessive thirst may be so extreme that the patient

drinks several liters of fluid daily. The amount of urine voided likewise may be great, amounting in extreme cases to as much as 7 or 8 liters or more in 24 hours. Daytime frequency and nocturia with five or six voidings which disturb sleep at night frequently are encountered. Loss of weight is common and may be considerable. Loss of strength is described by the patient as lack of endurance, lack of energy or "pep," or as being "tired all the time."

THE INCREASING LONGEVITY OF DIABETICS

Experience of George F. Baker Clinic, Boston, Massachusetts, 1897 to 1947



Excludes deaths within one week of first observation or hospital discharge.

Analysis by Metropolitan Life Insurance Company

FIG. 3. Expectation of life of diabetics at ages 10, 30 and 50 years in successive periods from 1897-1913 to 1939-1947.[58]

Disturbances in sexual function are more common in diabetes than might be inferred from most texts. In young females with inadequately controlled diabetes, menstruation may be absent or irregular. Those in whom the degree of control is definitely poor may not be fertile, but with only moderately well regulated diabetes the ability of young diabetic women to conceive appears to be little, if any, impaired. In the male, loss of sexual power usually is not a complaint except in

patients with diabetes of long-standing and particularly in those in middle life

Although most patients with diabetes probably develop symptoms sooner or later it must be emphasized that definite diabetes exists in a high percentage of cases with few or no symptoms Consequently in attempting to diagnose the disease the physician must not wait for symptoms to develop Success in the early detection of diabetes and in the avoidance of complications of the disease depend upon early diagnosis by routine tests of the blood and urine at an early stage before symptoms appear

In most diabetic patients, particularly in those in middle life and beyond the time of onset of diabetes can be determined only with difficulty because of the gradual and insidious development of the condition Rarely indeed is the onset sudden or rapid, much more commonly it is gradual or indefinite

Physical Signs

Except possibly in acidosis and coma there are no characteristic physical signs by which one can identify the diabetic with certainty The average patient, who presents himself to the physician for the first time is a middle aged individual more commonly a woman who although he or she may have lost some weight still is heavier than the average for age and height The skin and mucous membranes may be dry, reflecting varying degrees of dehydration In the rare case small raised nodules with a yellowish top may be found scattered throughout the skin representing xanthomata The eyes may show simple transient refractive errors or there may be retinitis or cataracts In the middle-aged or elderly patient, however, it is difficult or impossible to say to what extent the ocular disturbances are due to diabetes The examination of the cardiovascular system may yield normal findings although as has been pointed out, the incidence of arteriosclerosis and hypertension are relatively greater in diabetics than in non diabetics of comparable age and sex In certain groups of diabetics the incidence of pulmonary tuberculosis is higher and there is ample justification for routine chest x-rays for diabetics In the absence of complications the examination of the abdomen is essentially normal, although not infrequently the liver may be felt

The physical examination of the diabetic should be thorough including not only the heart, lungs, abdomen and blood pressure but also the teeth, ocular fundi, rectum and in female patients, the pelvis. Not to be forgotten is a careful examination at each visit of the feet and lower legs because of the well known tendency to impaired circulation in the lower extremities. The legs should be examined carefully for pulsations in the dorsalis pedis and posterior tibial and, if lacking in these, in the popliteal and femoral vessels. The feet should be examined as to cleanliness and the presence of epidermophytosis, corns, calluses and ulcerations or breaks in the skin.

Diagnosis

Although the symptoms and to a less extent the physical findings may lead one to suspect diabetes, final proof as to diagnosis depends upon information obtained in the laboratory. The safest rule in the treatment of a patient with sugar in the urine is to assume that diabetes is present until proven otherwise. However, adherence to this rule should not imply delay in taking active steps to establish an accurate diagnosis. The following classification of individuals with sugar in the urine (melituria) has proved useful with large numbers of patients[8].

Classification of Meliturias

(1) *Diabetes mellitus* is present if the venous blood sugar is 130 mgm. per 100 c.c. or above in the fasting state or 170 mgm. or above following the taking of food or glucose. If capillary blood is used one may arbitrarily take a figure of 200 mgm. per 100 c.c. or above following food or glucose as diagnostic, allowing thereby an average of 30 mgm. per 100 c.c. for the capillary venous difference customarily seen postprandially. The figures mentioned refer to those obtained by Folin's methods of analysis in which in addition to "true" blood sugar a non glucose reducing fraction corresponding on the average to 15 to 25 mgm. per 100 c.c. (often considerably more) must be allowed for. The standards given are of course arbitrary and subject to criticism. All will agree, however, that the fasting value of 130 mgm. is safe. Some believe that the figure of 170 mgm. after food or glucose is too strict a

standard, but experience with large numbers of patients over years of time has lent reliability to this value

(2) By *potential diabetes* is meant a condition in which glycosuria varies with and is dependent upon, diet, and in which blood sugar values, although somewhat above the average normal do not quite reach those arbitrarily chosen for the diagnosis for diabetes This is at times a most useful category particularly in individuals with diabetes in close relatives and whom it is desired to keep in a group readily available for continuous observation

(3) *Renal glycosuria* is not a disease in the true sense of the word but a condition in which the renal threshold for sugar is below the average normal Some clinicians make the diagnosis of renal glycosuria in any individual with a lowered threshold It is helpful however, to restrict the number of patients with whom this diagnosis is made by requiring that the renal threshold for sugar be so low that sugar appears in the urine constantly even with the individual in the fasting state This means of course that in such cases the renal threshold is in the neighborhood of 100 mgm of sugar per 100 c c of blood Renal glycosuria is asymptomatic with the possible exception of the easy fatigability and lassitude complained of by some patients It requires no treatment

(4) *Unclassified glycosuria* is a term applied to the condition in those individuals with glycosuria who cannot be fitted into the above three groups and includes a wide variety of conditions with which small amounts of glucose in the urine may be associated

(5) *Melituria Other Than Glycosuria* —In this group are included patients with lactosuria fructosuria galactosuria and sucrosuria Further discussion of the non diabetic meliturias will be found in Chapt V-A which follows this one

Diagnostic Studies

When a patient presents himself at the physician's office or clinic, the opportunity should be seized at once to obtain specimens of urine and blood for sugar without regard to relationship to food The time of the blood sugar and the time and composition of the last meal should be recorded carefully It is unwise to neglect to take such specimens at the first visit and to let the patient go with instructions to bring in a specimen the following morning or at some other time If the urine

contains sugar and yet the random blood sugar is within normal limits then the patient should be asked to return for an examination of the blood and urine at 45 to 60 minutes after the completion of a regular meal An alternative at the first visit is to give the patient 50 grams of glucose and to secure a single blood and urine sample 45 minutes later If the patient has not been on a previously restricted diet and has not been taking insulin this is a justifiable procedure which often will allow the diagnosis to be made without delay so that treatment may be begun

If however the above steps do not allow a definite diagnosis then recourse to a formal glucose tolerance test must be had It must be emphasized however that the physician s first thought must not be a glucose tolerance test Instead single blood sugar tests made at random or within an hour after meals should be made first and if diagnosis is possible by such means the patient should be spared the expense inconvenience and possible temporary flare up of a diabetic condition which may be caused by *the giving of a large amount of glucose* *If a glucose* tolerance test is done it is important that the patient not have been on a restricted diet that he not be taking insulin and that he be free from infections thyrotoxicosis and other complications such as hepatic dysfunction which may cause a non diabetic to exhibit a diabetic type of glucose tolerance test curve The patient should have been following an unrestricted diet or one containing a minimum of 200 and preferably as much as 300 grams of carbohydrate daily for three or more days prior to the test

In carrying out the test the patient reports in the fasting state or not less than 8 hours after the taking of food Glucose may be given by mouth or by vein Although the intravenous route is preferable to the extent that factors related to absorption are ruled out in actual practice it is much easier for the average physician to arrange for the oral test and only in unusual cases will there be any significant difference in results As to the amount of glucose some have advocated the giving of 1 8 grams per kilogram of ideal body weight Experience has shown however that within rather wide limits the amount of glucose given is not of great importance and it is convenient to give arbitrarily a standard dose of 100 grams of glucose to adults Actually results obtained with 50 grams of glucose are only slightly lower than those obtained with 100 grams but the wealth of data in literature obtained with the 100 gram dose makes this larger amount preferable The

sugar is given in water in 20 per cent solution, flavored if desired with a little lemon juice

In children smaller amounts of glucose are desirable and for those weighing less than 100 pounds 1.8 grams per kilogram of body weight may be used For practical purposes one gram per pound of body weight yields about the same result and provides an easily remembered figure

Blood and urine samples are taken with the patient in the fasting state and at 1 1½ and 2 hours afterward Tests at 3 hours may be made if desired although rarely is the additional information of practical help Although there are many situations in which capillary blood samples are desirable and extremely helpful it is best not to base decisions as to diagnosis on capillary samples and far preferable to use venous blood At times as in small children the use of capillary samples for diagnosis cannot be avoided and in life insurance work capillary samples often are taken because of greater convenience

Three features must be considered in the interpretation of a glucose tolerance curve (a) the initial value (b) the peak value and (c) the value at the end of 2 hours All workers agree upon the importance of the initial value There is much disagreement, however, as to the relative importance of the height and the extent of the curve Some maintain that within certain limits it makes no difference how high the blood sugar rises following glucose provided it falls within 2 hours to the initial value or at least below 120 mgm per 100 c c Although there is much to be said for the importance of the two-hour value and this certainly must receive careful consideration the writer believes that diagnoses are best made on the basis of the peak value taking 170 mgm per 100 c c or above as abnormal when using venous blood It is possible that thereby some few individuals may be erroneously diagnosed as having diabetes but experience has shown that the number will be small indeed and that this is by far the safest policy

It must be emphasized that glucose tolerance tests are by no means infallible That tolerance for glucose may be influenced by a number of factors has already been stated Furthermore, as everyone familiar with laboratory procedures knows there is ample opportunity for errors to creep into the determination of the blood sugar unless all work is constantly under the watchful eye of a competent technician It is a good rule therefore that when the results of blood sugar determinations seem bizarre or inconsistent or do not fit clinical find-

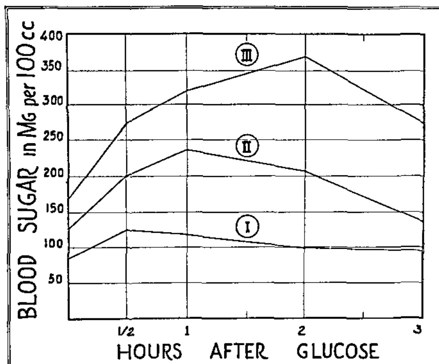


Fig 4 Three glucose tolerance curves The determinations were made on venous blood using the Folin Wu procedure (courtesy of Drs D Harting and C. C Bailey) Curve I represents the normal response to 100 grams of glucose given orally to a fasting subject (female aged 36 years) Curve II is that of a man aged 49 years with mild diabetes Curve III is that of a man aged 58 with moderately severe diabetes Following are the amounts of sugar found in the urine obtained during the tests (volumes of urine specimens not available)

		Hours after glucose			
	Fasting per cent	½ per cent	1 per cent	2 per cent	3 per cent
Curve I	0	0	0	0	0
II	0	0	1.4	3.3	0.8
III	1	3.0	7.5	[illegible]	7.0

ings interpretation of the results be made with reservations and the test repeated at a later date

If the glucose tolerance test gives normal results and if the patient continues to exhibit meliturıa then active steps should be taken to determine the type of sugar excreted These steps will be outlined in detail in the chapter on Non diabetic Meliturıa

Exton-Rose Test—Mention is necessary of the one hour two dose glucose tolerance test devised by Exton and Rose[57] In this procedure following the obtaining of initial urine and blood specimens for sugar content, the fasting subject is given 50 grams of glucose by mouth Thirty minutes later specimens of urine and blood are taken again for sugar determinations Immediately afterward a second lot of 50 grams of glucose is given Then 30 minutes later, or one hour after the beginning of the test a third set of urine and blood tests is taken As originally described the results were considered within normal limits if, following the second administration of glucose the third blood sugar either fell or did not rise more than 10 mgm higher than the second The procedure was designed principally for life insurance work to minimize inconvenience to the subject and was carried out usually with capillary blood Although the test has been used considerably, it has not found general acceptance and seems to have few or no advantages over the standard glucose tolerance test If used the peak value appears to be the most helpful in diagnosis

Laboratory Procedures

Every physician who takes the responsibility of treating patients with diabetes should have access to a good laboratory where the necessary determination of constituents of the blood and urine may be carried out quickly and reliably Facilities should be available in a hospital laboratory or some other central laboratory for the obtaining of emergency tests at any time nights Sundays and holidays With no other major disease it it so important that the physician and patient receive constantly the assistance and support of the laboratory

No attempt will be made here to give in detail the results of laboratory procedures since these are to be found in standard texts and manuals However it seems worth while to state briefly the procedure for testing for sugar in the urine by the Benedict test, by all odds the best of the methods Benedict s solution is stable and the test is easily carried out and interpreted The procedure is as follows

In a test tube place 8 drops of urine and 5 c c (one teaspoonful) of Benedict s solution (4 drops of urine and 2 5 c c of Benedict s solution may be used if desired) Place the tube in boiling water and allow to remain for 5 minutes in the water kept boiling At the end of that time take the tube

out shake and read the result If no sugar is present the color and appearance will be unchanged from the clear blue of the Benedict s solution Increasing amounts of sugar are indicated by light green yellow green yellow orange or brown and red tests

In recent years various modifications of standard methods have been devised to lessen the time and apparatus required to carry out the test for sugar in the urine Some of these such as the Clinitest and the Galatest * have proved useful and have shown themselves to be reliable if carried out according to instructions However the standard Benedict test as described above should be familiar to every diabetic patient

The determination of the percentage of sugar in the urine daily is a desirable procedure in the office or hospital laboratory and promotes care in regulation of the diabetic condition One need not use a time and material consuming method since with care accurate results can be obtained with Smith s modification of Benedict s method[4] Particularly if adapted for use with the photoelectric colorimeter another convenient procedure for use when large numbers of determinations are to be made regularly is that of Sumner as modified by Exton[5] Approximate values for the percentage of sugar in urine can be obtained by the Clinitest apparatus previously mentioned

In almost all situations testing of the urine using a 10 per cent aqueous solution of ferric chloride (Gerhardt test) suffices for the detection of acetone bodies Experience has shown that it is best not to burden the patient with this procedure since often misinterpretation confusion and undue worry may result The test is to be carried out as follows

To 5 or 10 c c of urine in a test tube add several drops of a 10 per cent aqueous solution of ferric chloride If diacetic acid or acetone is present a reddish or port wine color will result the intensity varying with the amount of acetone bodies present Since certain drugs notably aspirin may give a falsely positive result routinely one should pour half the contents of the tube into another test tube Then one tube should be placed in boiling water for five minutes and compared with the tube not so heated Since the acetone bodies are volatile the heated tube will appear lighter in color if the positive test was due to acetone bodies If the reddish color does not disappear on boiling or becomes deeper it is possible that the test was falsely positive

* Clinitest apparatus and tablets are made by The Ames Co Elkhart Ind
Galatest is made by the Denver Chemical Mfg Co New York N Y

In this instance the presence or absence of acetone bodies should be determined by the use of the Rothera test carried out as follows

To approximately 5 c.c. of urine in a test tube add to the point of saturation a few grams of a mixture prepared by intimately grinding to a fine powder 5 grams of sodium nitroprusside and 00 grams of ammonium sulfate Shake the tube thoroughly to mix the urine and the powder Then by tilting the tube overlay with a small quantity of strong ammonia water A purple band of varying intensity will form at the junction of the two liquids if diacetic acid and acetone are present At the end of or 3 minutes the maximum color appears and the test should be read If preferred the test may be done in the following manner

Add 1 to c.c. of 10 per cent acetic acid and a small crystal of sodium nitroprusside to 5 c.c. of urine in a test tube Shake add 2 to 3 c.c. of strong ammonia water and shake again or carefully overlay with strong ammonia water A purple color or purple band indicates the presence of diacetic acid and acetone

Blood sugar may be determined by a number of good methods such as those of Folin-Wu Shaffer-Hartmann, Somogyi and Hagedorn Jensen Details of these procedures will be found in standard texts In reporting blood sugar results it is important to state the type or procedure used in the determination since some such as the Nelson procedure[9] give values representing more nearly true glucose and others such as the Folin Wu method determine a variable amount (15 to 25 mgm per 100 c.c. or more) of non-glucose reducing substances There can be no doubt but that true blood sugar methods are preferable and it is to be hoped that in the future a general shift may be made to such procedures

The use of capillary blood as obtained from an ear lobe or finger tip is much to be encouraged particularly when dealing with children or in situations in which frequent blood samples are imperative In interpreting capillary values one must keep in mind the capillary venous difference already referred to

In recent years it has become increasingly apparent that the problem in diabetes consists not only in the treatment of the disease itself but of its complications Consequently in the diagnosis and treatment of complications seen in diabetics there is a growing need for facilities for the determination of other constituents of blood and urine Particularly helpful at times are determinations of the concentration of urea and nonprotein nitrogen chlorides, carbon dioxide (content or combining power) sodium potassium and protein in the blood Methods of analysis will be found in standard laboratory texts

Treatment of Uncomplicated Diabetes

General Plan of Treatment

Most patients with uncomplicated diabetes can be treated successfully by periodic visits to the doctor's office or out patient clinic provided adequate facilities exist for laboratory studies and instruction of the patient In recent years due to the shortage of hospital beds it has become increasingly necessary that a large proportion of diabetic patients be treated in this fashion However there is no doubt that patients at the outset of treatment do better if they can spend a week in a hospital where facilities exist for carefully weighed diets necessary laboratory studies and intensive classroom and personal instruction Often it has been said that with diabetes the patient who knows the most lives the longest There is much truth in this and if it is impossible for patients to initiate diabetic treatment with a course of instruction in a hospital it is incumbent upon the doctor either in his office or in the out patient clinic to provide both group and individual instruction Matters pertaining to diet urine testing insulin administration and avoidance of complications must be explained again and again in simple language to patients This is a formidable task for the private physician and even for the out patient clinic it requires for successful carrying out the aid and cooperation of nurses dietitians social service workers laboratory technicians and secretaries If the patient is admitted to a hospital for a week for regulation and instruction it is imperative that he not be kept in bed but that he be allowed his street clothes and to be up and around securing in so far as possible an amount of exercise which simulates that ordinarily obtained at home

With hospital patients the food should be weighed carefully before and after meals and that not eaten subtracted from the amount prescribed In appropriate columns on a composite chart are recorded daily the amounts of carbohydrate protein fat and calories consumed per day On this same chart are recorded daily the volume of urine voided in 24 hours the results of diacetic acid or acetone tests and the percentage and total number of grams of sugar excreted during the 24 hour period Likewise space should be provided for the recording of results of qualitative tests for sugar in urine before meals and at bedtime In other columns should be listed results of relevant blood tests such as those for sugar nonprotein nitrogen and carbon dioxide

content. Likewise space is necessary for recording insulin doses as ordered and as given together with the time of administration. A chart of this type, particularly if it allows space also for results of other routine and special tests of the blood and urine and room for doctors' notes, is invaluable for the physician treating a diabetic patient. It provides on one sheet all the data necessary and avoids endless leafing through of bulky records for the information desired.

Blood for the determination of its sugar content, contrary to usual hospital practice, should be drawn not only before breakfast but also at other times of day as indicated. Valuable information may be obtained from the fasting blood sugar, and with patients taking protamine zinc or NPH insulin this value is the best single index of the adequacy of the dose of this type of insulin. However, it is often helpful to know the blood sugar just before the noon meal, since this value is the best index of the effect of unmodified (regular or crystalline) insulin taken in the morning before breakfast. Also helpful at times is a knowledge of the blood sugar in the late afternoon. For purposes of diagnosis, particularly in mild cases, the blood sugar at one hour after a meal is the most helpful. Blood for determination of sugar may be placed in bottles containing a flouride oxalate mixture* as an anticoagulant so as to preserve the sugar content until the determination may be made. The physician will do well to make use of capillary blood samples whenever possible, since these present a minimum of inconvenience to the patient and allow more frequent estimations than one would feel justified in using with venous blood.

Patients should be taught that the best single test of urine during the day is the one in the morning before breakfast, because with all patients (except those very few with an extremely low renal threshold) it is proper to insist that this test, performed on a fresh specimen, should be sugar-free or, at most, give only a light green test with Benedict's solution. With patients taking protamine zinc or NPH insulin the test before breakfast becomes a reliable guide as to the adequacy of the dose of this variety of insulin. Patients should be taught that tests at home should, in general, be carried out before rather than after, meals. Positive tests an hour or two after meals may represent "overflow" glycosuria. With patients taking protamine zinc or NPH insulin a test at bedtime is important, usually it is advisable to allow slight

* 5 parts neutral sodium fluoride to 2 parts powdered potassium oxalate; use approximately 14 mgm. per c.c. of blood.

glycosuria at bedtime to insure freedom from hypoglycemia during the night

The most accurate test is that of the 4 hour amount specimen and with hospital patients this should be carried out daily so that the number of grams excreted may be ascertained At home it is usually not convenient to make complete 4 amount collections but this is often possible once a week or at such intervals as will give the information desired

Diet

The basis of all diabetic treatment must be a carefully planned diet Dietary restrictions should be explained in positive terms the patient should be told what to eat rather than given blanket instructions as to what to avoid In planning a diabetic diet the best approach is to regard it as a modification of a normal diet keeping in mind not only the proportions of carbohydrate protein and fat but also the necessity for including adequate amounts of vitamins minerals roughage and fluid The average normal adult consumes between 1 600 and 3 000 calories a day Textbook figures in this regard are apt to err on the side of being too high and certainly one sees many middle aged persons leading sedentary lives who maintain their weight and strength on diets providing 1 600 to 000 calories Individuals doing strenuous work may require , 000 to 4 000 calories a day Adults on an unselected diet consume daily 00 to 400 grams of carbohydrate 60 to 1 0 grams of protein and 60 to 1 0 grams of fat

Carbohydrate—It is carbohydrate that the diabetic tolerates least well and it is difficult indeed for even a patient with well regulated diabetes to consume sugar or sweets without excreting sugar in the urine in the hour or two afterward Experience has convinced most clinicians that all diabetics do well to avoid completely sugar sweets pastries and other foods containing appreciable amounts of sugar as such Furthermore most diabetics get along better if foods rich in starch are definitely limited for example bread should be restricted usually to one slice (30 grams) at a meal and potato or its equivalent to one average serving at one meal a day These restrictions mean that the average diet contains 150 to 00 grams of carbohydrate and rarely does one need to prescribe more than 00 grams except with

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5 parts neutral sodium fluoride to parts powdered potassium oxalate use approximately 14 mgm per c c of blood

activity and the maintenance of body weight is difficult to state exactly because of great variation from one person to another With diabetic patients one commonly allows 35 to 40 calories per kilogram of ideal body weight for persons engaged in moderate physical activity and 30 calories per kilogram of ideal body weight for those doing light work A man weighing 70 kg (154 pounds) and engaged in light activity may be allowed 2100 calories a day, and this might well be provided by 200 grams of carbohydrate 100 grams of protein and 100 grams of fat As already noted one often finds that women engaged in light housework about the home maintain weight and strength on diets furnishing only about 25 calories per kilogram of body weight or 1600 to 1 800 calories a day It is true that at home the diet as actually eaten by the patient may be higher in fat and in calories than the patient realizes Often it is forgotten that fat used in the cooking and preparation of food increases the caloric content just as do butter or other fats added at the table For this reason diabetics should be encouraged to eat simple foods simply prepared

Prior to the onset of diabetes most adult diabetic patients are overweight and often greatly so In the present day even at the time that they report to the physician the majority are definitely overweight In planning the diet the physician must take great care to limit the number of calories to the level at which the overweight patient will gradually lose This loss of weight usually will exert beneficial effect upon the diabetic condition to say nothing of the favorable influence regarding other complicating conditions such as hypertension and heart disease The diabetic patient should be taught over and over again the peril of obesity and encouraged to keep his weight at or near the level which standard tables show to be the average for his age and height

Calculation of Diets—The calculation of diets diabetic or otherwise need not be a complicated process Procedures have been simplified greatly in recent years In the pre insulin days a great deal was said about the total glucose content of the diet and various formulae were made in an attempt to estimate how much fat could be prescribed without danger of causing ketosis Woodyatt assumed that 1 5 grams of fatty acid could be allowed safely per gram of total glucose Now that diets are much higher in carbohydrate and in fact approach normal diets in composition such calculations are rarely necessary

In 1950 a booklet entitled Meal Planning with Exchange Lists was

children or with those engaged in strenuous activity in which case the amount of carbohydrate allowed may be as much as 250 grams a day. With liberal carbohydrate allowances care must be taken not to use bread, potato and other high carbohydrate foods to the exclusion of vegetables, fruit and milk which have great value because of their vitamin and mineral content.

Diets as prescribed in recent years are much more liberal than in the days before insulin, and it is the general consensus that patients feel better and do better with the larger allowance of carbohydrate. Some clinicians have gone so far as to prescribe diets containing 300 to 400 grams of carbohydrate a day, and others have imposed little or no restrictions on patients' natural desires, allowing so called "free diets." The higher carbohydrate diets have the disadvantage that in order to fill the dietary prescription and still keep the bulk of food to a reasonable amount, foods rich in sugar such as jellies must be used. "Free diets" are to be deplored because they provide no systematic basis of treatment.

Protein.—Although there has been considerable argument as to the optimal amount of carbohydrate in the diabetic diet, there is general agreement as to the amount of protein required. Adults should receive 2/3 to 1 gram of protein per kilogram (2.2 pounds) of ideal body weight. In practice this means that the average diet should contain from 60 to 100 grams and up to 120 grams of protein a day. In growing children the amount of protein provided must be greater, even as much as 4 grams per kilogram of body weight at the earlier ages. In all patients one must adjust the amount depending upon the age, weight, sex, occupation, complicating conditions and dietary preferences of the patient.

Fat and Calories.—When one has arrived at the amount of carbohydrate and protein to be allowed daily, one makes up the balance of the calories by means of fat. The decision as to the amount of fat and calories depends upon the age, sex, occupation and body weight of the individual. Patients who are overweight will do better with the allowance of fat reduced to 50 or 60 grams a day. Underweight patients require as much as 100 to 120 grams or more a day. Of the three classes of foodstuffs, fat has the least direct effect upon hyperglycemia and glycosuria, although the possible role of lipids and cholesterol in the production of arteriosclerosis must be kept in mind.

The number of calories required for basal energy and heat, physical

in favor of the accurate weighing of food at least in hospitals Patients will benefit greatly from being taught how to use gram scales and they should be encouraged to purchase scales and to weigh their food at home for a few weeks at the beginning of treatment In this way the hand and eye become trained as to the weight of various foods and when weighing is discontinued the patient can carry on very well indeed by estimating amounts on the basis of his training At intervals or when a new type of food is used there should be a return to weighing If scales are not used then the next best is the use of food models blocks or cards and in the hands of careful patients these may yield good results Less accurate than this is the use simply of household measurements in terms of teaspoons tablespoons measuring cups and small medium and large servings The last named plan will be successful in so far as the patient conscientiously interprets the rather general instructions given

There are many patients with mild diabetes with whom adequate control of the condition may be secured by the simple exclusion of sugar sweets and pastries and the limitation of carbohydrate rich foods as already discussed With such patients a sample diet would include the following at *breakfast* one egg with or without bacon a small serving of cereal with two ounces of light cream fruit such as a medium orange or one half grapefruit one slice of toast with butter and coffee or tea as desired In general terms the *noon* and *evening* meals would consist of clear soup if desired medium serving of meat fish cheese or eggs liberal quantities of 5 per cent (leafy green) vegetables one medium serving of a 10 per cent vegetable (see Table V) a medium serving of fresh fruit for dessert one slice of bread butter and coffee or tea as desired In addition to the above 1/2 to 1 pint (8 to 16 ounces) of milk may be allowed throughout the 24 hours and a total of 1/4 pint (4 ounces) of light cream It is obvious that more specific instructions as to the diet must be based upon the body build and needs of the individual A diet such as that just outlined will furnish from 140 to 170 grams of carbohydrate a day

Timing of Diet and Distribution of Food—It is common practice to allow 1/5 of the day's allowance of carbohydrate at breakfast 2/5 at the noon meal and [illegible]/5 at the evening meal With patients taking protamine zinc insulin enough carbohydrate is withheld from the noon and evening meals to allow a light lunch at bedtime containing 10 to [illegible]0 grams of carbohydrate With patients taking NPH insulin one gives

published by committees of the American Diabetes Association and the American Dietetic Association in cooperation with the Diabetes Branch of the U S Public Health Service Copies of this may be purchased from Health Publications Institute Inc Raleigh N C In this booklet with accompanying meal plan inserts basic information and outlines are provided for the use of the doctor and patient Although the methods of presentation and the classification of foods differ in details from those outlined in the discussion which follows the general plan is much the same and the aim is identical namely to present diet suggestions in a form easily understood and followed

To determine the 'total glucose' content of a diet one assumes that 100 per cent of the carbohydrate 58 per cent of the protein and 10 per cent of the fat are available as glucose on absorption by the body Thus a diet of C 200, P 100 F 100 would provide 200 grams of glucose from carbohydrate 58 grams from protein and 10 grams from fat or a total of 268 grams

To calculate the amount of fatty acid derived from a given diet one assumes that 100 grams of protein give rise to 46 grams and 100 grams of fat to 90 grams of fatty acid when metabolized The diet of C 200 P 100 F 100 would therefore provide 136 grams of fatty acid The fatty acid total glucose ratio would be 136/268 or 0 51

As basic facts the physician and patient must know that approximately 4, 4 and 9 calories (actually 4 1, 4 1 and 9 3) are furnished by the oxidation of 1 gram of carbohydrate protein and fat respectively

Dietary Prescription at the Beginning of Treatment—When a patient presents himself first for treatment the diet prescribed initially should be somewhat lower than that which will be required eventually This limitation of food will aid in bringing the diabetic condition under control However even at the outset of treatment starvation diets or diets extremely low in carbohydrate are unnecessary and may be harmful The average adult patient usually may be started on a diet providing 150 grams of carbohydrate and 70 grams of protein a day with the amount of fat adjusted to between 60 and 90 grams a day depending upon the body weight of the individual From this point on increases or decreases in the various components of the diet may be made depending upon the diabetic condition and the behavior of the patient s weight

With the adoption of more liberal diets the weighing of food has been given up by some clinicians However, there is much to be said

they are sufficiently accurate and representative to allow use with assurance

TABLE V

VEGETABLES ARRANGED IN GROUPS ACCORDING TO THEIR APPROXIMATE CARBOHYDRATE CONTENT

5 Per Cent

1 3 Per Cent
- Lettuce
- Cucumbers
- Spinach
- Asparagus
- Rhubarb
- Endive
- Marrow
- Sorrel
- Sauerkraut
- Beet greens
- Dandelions
- Swiss chard
- Celery
- Mushrooms

10 Per Cent
- String beans
- Brussel sprouts
- Pumpkin
- Turnip
- Squash
- Okra
- Beets
- Carrots
- Onions
- Green peas very young

3 5 Per Cent
- Tomatoes
- Water cress
- Sea kale
- Cauliflower
- Egg plant
- Cabbage
- Radishes
- Leeks
- String beans very young
- Broccoli
- French artichokes
- Green peppers
- Summer squash
- Kohlrabi

15 Per Cent
- Green peas
- Jerusalem artichokes
- Parsnip
- Lima beans young

20 Per Cent
- Potato
- Shelled beans
- Lima beans
- Green corn
- Boiled rice
- Boiled macaroni

Note that the carbohydrate content of the vegetables in the 5 per cent group is reckoned as 3 per cent and those in the 10 per cent group as 6 per cent

It will be noted that in Table IV the terms 5 per cent and 10 per cent vegetables are used A listing of these and also those of 15 and 20 per cent carbohydrate content are given in Table V This classification gives as good results as those which divide vegetables into groups of 3 6 9 12 15 and 18 per cent per carbohydrate A simple listing of the number of grams of fresh or water packed fruit required to yield 10 grams of carbohydrate is given in Table VI In the teaching of patients orange pulp or orange juice is taken as the fruit of preference

in addition 10 to 15 grams of carbohydrate in the mid-afternoon This manner of distribution of food need not be strictly adhered to and with many patients it may work out best to provide 1/3 of the carbohydrate at each of the three meals making due allowance of course, for lunches at bedtime and perhaps in the forenoon and afternoon With patients

TABLE IV

THE APPROXIMATE CARBOHYDRATE, PROTEIN FAT AND CALORIC CONTENT OF VARIOUS FOODS CALCULATED PER 30 GRAM (1 OUNCE) PORTIONS*

30 gm (1 ounce) contain approximately	*Carbohydrate gm*	*Protein gm*	*Fat gm*	*Calories*
Vegetables 5 per cent	1	0 5	0	6
Vegetables 10 per cent	2	0 5	0	10
Potato	6	1	0	28
Bread	18	3	0	84
Crackers in square 4	0		2	106
Oatmeal dry wgt	0	5	2	118
Milk	1 5	1	1	19
Meat cooked lean	0	8	5	77
Fish fat free	0	6	0	4
Chicken cooked lean	0	8	3	59
Egg one	0	6	6	78
Cheese	0	8	11	131
Bacon	0	5	15	155
Cream 20 per cent	1	1	6	6
Cream 40 per cent	1	1	1	116
Butter	0	0	25	225
Oil	0	0	30	270

This table as well as Tables V and VI are adapted from Joslin and associates[8]

taking protamine zinc or NPH insulin best success is achieved if food is spread out more evenly over the waking part of the 24 hours

Diet Prescriptions—There are various good approaches to the writing of a diet prescription *In the following remarks and in the* accompanying tables will be presented simple methods which have been found useful with large numbers of patients of all ages and levels of intelligence and economic status In Table IV is given a basic list of foods expressed in general terms with the approximate amount of carbohydrate protein fat and calories per 30 grams (one ounce) It is obvious that the figures given cannot be regarded as strictly accurate because of the wide variation of composition of foodstuffs However

they are sufficiently accurate and representative to allow use with assurance

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5 Per Cent

1 3 Per Cent
Lettuce
Cucumbers
Spinach
Asparagus
Rhubarb
Endive
Marrow
Sorrel
Sauerkraut
Beet greens
Dandelions
Swiss chard
Celery
Mushrooms

10 Per Cent
String beans
Brussels sprouts
Pumpkin
Turnip
Squash
Okra
Beets
Carrots
Onions
Green peas very young

3 5 Per Cent
Tomatoes
Water cress
Sea kale
Cauliflower
Egg plant
Cabbage
Radishes
Leeks
String beans very young
Broccoli
French artichokes
Green peppers
Summer squash
Kohlrabi

15 Per Cent
Green peas
Jerusalem artichokes
Parsnips
Lima bean ung

20 Per Cent
Potato
Shelled beans
Lima beans
Green corn
Boiled rice
Boiled macaroni

Note that the carbohydrate content of the vegetables in the "5 per cent group is reckoned as 3 per cent and th e in the 10 per cent." group as 6 per cent

It will be noted that in Table IV the terms 5 per cent and 10 per cent vegetables are used A listing of these and also those of 15 and o per cent carbohydrate content are given in Table V This classification gives as good results as those which divide vegetables into groups of 3 6 9 1 15 and 18 per cent per carbohydrate A simple listing of the number of grams of fresh or water packed fruit required to yield 10 grams of carbohydrate is given in Table VI In the teaching of patients orange pulp or orange juice is taken as the fruit of preference

since it contains on the average about 10 per cent carbohydrate Patients should be encouraged to take as their fruit at least at one meal a day an orange or one half grapefruit because of their relatively low carbohydrate value and the high vitamin C content

TABLE VI

APPROXIMATE CARBOHYDRATE SUBSTITUTION VALUES FOR VARIOUS FRUITS FRESH OR CANNED (WATER PACKED) SHOWING THE NUMBER OF GRAMS OF EACH REQUIRED TO YIELD 10 GRAMS OF CARBOHYDRATE

Grapefruit pulp	150	Raspberries	80
Strawberries	150	Plums	80
Watermelon	150	Honeydew melon	70
Cantaloupe	150	Pineapple	70
Blackberries	1[illegible]0	Apple	70
Orange pulp	100	Blueberries	[illegible]0
Pears	90	Cherries	60
Peaches	90	Banana	50
Apricots	80	Prunes (cooked)	50

(Commercial ice cream allowed occasionally as a substitute for fruit may be regarded as roughly 20 per cent carbohydrate)

With Tables IV, V and VI giving basic information one is prepared to plan a diet according to a given prescription A sample diet with the calculations made in detail is shown in Table VII Here will be noted that in the case of most foods multiples and fractions of 30 grams (one ounce) are prescribed so as to make calculations easier with the use of values in Table IV In actual practice vegetables in the 1 to 3 per cent group (see Table V) may be allowed freely, leafy-green vegetables such as lettuce, celery and spinach, consist almost entirely of water and fiber and have little or no food value

In Table VIII are listed six diets providing for amounts of carbohydrate from approximately 120 to 200 grams a day The corresponding protein values range from approximately 50 to 100 grams, fat from approximately 60 to 120 grams and calories from about 1300 to 2300 a day Such a table is often of help as a guide and timesaver to the physician or dietitian who is planning a diet

Intelligent patients should be taught the rudiments of diet calculation or at least should be instructed carefully as to allowable substitutions of food which can be made at home They should be given a sheet containing information such as that in Table IX in which food

TABLE VII

DIET SUITABLE FOR CERTAIN ADULT DIABETIC PATIENTS SHOWING CALCULATIONS IN DETAIL

	Household Measure	*Grams*	*Carbohydrate*	*Protein*	*Fat*	*Calories*
Breakfast						
Orange	1 medium	150	15	0	0	60
Egg	one		0	6	6	78
Oatmeal (cooked)	*small serving*	1 0	10	3	1	61
Cream 20 per cent	ounces	60	2	2	12	124
Bread	1 slice	30	18	3	0	84
Butter	2 teasp	10	0	0	8	7
	Total		45	14	27	419
Lunch						
Lean Meat	medium serving	75	0	20	12	188
Vegetables 5	freely	150	5	2	0	28
Vegetables 10	1 medium serving	75	5	1	0	4
Bread	1 slice	30	18	3	0	84
Butter	2 teasp	10	0	0	8	7
Cream 0 per cent	1 ounce	30	1	1	6	6
Orange	1 medium	150	15	0	0	60
Milk	6 ounces	180	9	6	6	114
	Total		53	33	3	63
Supper						
Lean Meat	medium serving	75	0	0	12	88
Vegetables 5	freely	150	5	2	0	28
Vegetables 10	1 medium serving	75	5	1	0	24
Potato	1 medium	75	15	3	0	7
Bread	1 slice	30	18	3	0	84
Butter	teasp	20	0	0	27	153
Cream 0 per cent	1 ounce	30	1	1	6	6
Orange	1 medium	150	15	0	0	60
	Total		59	30	35	671
Bedtime Lunch						
Crackers m 51	2	15	10	1	1	53
Milk	6 ounces	180	9	6	6	114
	Total		19	7	7	167
Grand total			176	84	101	1949

NOTE In the above diet for sake of simplicity foods are expressed in general terms Instead of oatmeal an equivalent amount of any cereal dry or cooked may be used In place of orange equivalent amounts of other fresh fruit may be substituted (see table VI) In place of meat one may use fish cheese or eggs in quantities yielding approximately the same amounts of protein and fat Note that the average carbohydrate content of the 5 per cent vegetables is taken as 3 per cent and of the 10 per cent vegetables as 6 per cent

TABLE VIII

DIABETIC DIETS

Diets	TOTAL DIET Carbohydrate	Protein	Fat	Calories	CARBOHYDRATE (C) 5% Vegetables	Orange	Oatmeal	Potato	Bread	PROTEIN and FAT (PF) Milk	Egg	Meat	Bacon	20% cream	Butter
C1 PF1	121	53	64	1276	300	400	15	90	45	40	1	75	—	120	15
C2 PR	136	60	71	14 3	,00	400	15	1 0	60	40	1	90	—	1 0	0
C3 PF3	151	,0	80	1604	300	400	15	150	75	40	1	1 0	—	1 0	5
C4 PF4	165	82	97	1861	300	450	15	150	90	40	1	1,50	15	120	30
C5 PF5	180	89	103	003	300	450	15	180	105	240	1	165	15	1 0	35
C6 PF6	199	99	123	299	300	450	30	180	1 0	40	1	180	30	1 0	45

All of the above diets include two crackers (2½ in square) and 1 0 gms milk at bedtime

Diets	Carbohydrate	Protein	Fat	Calories	5% Vegetables	Orange	Oatmeal	Potato	Bread	Milk	Egg	Meat	Bacon	20% cream	Butter
Acute illness	152	50	52	12,6			15		90	960	1				15

Approximate equivalents 1 small orange (100 gms) = ½ banana (50 gms) = ½ saucer oatmeal (15 gms dry or 120 gms cooked) = 2 large saucers (300 gms) 5% vegetables = 1 large saucer (150 gms) 10% vegetables = potato size of egg = ½ slice (15 gms) bread

substitutions most commonly desired are set down in some detail. Patients quickly learn that 30 grams are equivalent to one ounce and in the substitution of foods even though they do not use scales learn to make selections with considerable accuracy. As has been stated before patients should be encouraged to buy gram scales and at least at the outset of treatment to weigh their food. The most desirable scales are those with a movable dial which permit the rapid taring of containers.

TABLE IX

LIST OF FOODS SHOWING AMOUNTS NECESSARY TO YIELD APPROXIMATELY 10 GRAMS OF CARBOHYDRATE

Food	*Household Measure*	*Weight Gm*
Sugar	2 lumps	10
Orange juice	3 ounces	100
Banana	1	50
Milk	6 ounces	180
Ginger ale	3 ounces	100
Crackers in square	2	15
Crackers in in d	4	15
Bread	slice	15
Oatmeal (cooked)	saucer	120
Other cooked cereal	saucer	104
Dry cereal	Small serving	1
Shredded wheat biscuit		15
Potato	1 small	50

Vitamins.—By virtue of the fact that the diabetic diet contains an abundance of fruits and vegetables and adequate amounts of protein foods it is apt to be more nearly an adequate diet as regards protein vitamins and minerals than that of the average person in the general population. The physician or dietitian must keep this prominently in mind and in planning the diet for a given diabetic must insure that it is entirely adequate in every respect. Recommended daily dietary allowances of vitamins and minerals as estimated by the Committee on Foods and Nutrition may be found in publications of the National Research Council.

Vitamin A is found in abundance in fish liver oils butter-fat milk, egg yolk and to a lesser extent in the leaves of food plants. Certain foods such as green vegetables and carrots contain carotene which is transformed to vitamin A in the body.

The *vitamin B* complex includes thiamine niacin, riboflavin, pyridoxine pantothenic acid, paraminobenzoic acid, inositol, biotin, choline and folic acid Of these thiamine (vitamin B_1) is of especial importance in carbohydrate metabolism When thiamine is deficient, the products of carbohydrate metabolism as pyruvic acid accumulate in the blood and tissues The pyrophosphoric acid ester of thiamine is the enzyme cocarboxylase, its presence in adequate amounts is necessary for the oxidation of pyruvic acid Because of the recognized influence on carbohydrate metabolism there have been claims of a specific beneficial effect of giving large doses of thiamine or of vitamin B complex to diabetic patients It has been stated that by giving large amounts the diabetic condition may be improved to the extent that insulin may be lowered in dosage or even given up entirely One must regard such reports with skepticism It has been the finding of most clinicians that, unless one is dealing with a patient with obvious signs of vitamin B deficiency rarely is there a dramatic or striking effect on the diabetic condition or the insulin requirement This statement should not be taken to belittle the importance of vitamin B or of the giving of vitamin supplements in appropriate cases Vitamin B_1 (thiamine) is found in whole grain cereals, eggs meat yeast and to some extent in fruits and vegetables Vitamin B or G (riboflavin and niacin) are found in yeast, liver eggs milk lean muscle meat and in green leaves of plants Patients should be encouraged to select whole grain cereals and breads in order to maintain an adequate intake of vitamin B especially thiamine

Vitamin C (ascorbic acid) is found in abundance in citrous fruits and tomatoes and in smaller quantities in other raw fruits and vegetables particularly strawberries and cabbage Fortunately the diabetic diet supplies these foods in abundance

Vitamin D is present in large amounts in fish liver oils and in varying amounts in foods irradiated with ultra-violet light The short ultra violet rays of the sun convert 7 dehydrocholesterol of the skin into active vitamin D

Vitamin E (tocopherol) occurs in most foods and hence is rarely, if ever, lacking in unselected diets Its richest source is wheat germ oil, but it is present in considerable amounts in other seed-germ oils. Although its lack in animals may lead to sterility the role of vitamin E in human nutrition is at present not settled

There are many diabetic patients who will benefit by taking supplementary vitamins, particularly those of the B complex However,

often one is working in an unknown field and in the usual case one is unable to decide with certainty as to whether or not vitamin supplements are truly effective The requirement of diabetics for vitamins may be somewhat greater than that of non diabetics Undoubtedly throughout the country, there is a tremendous amount of unnecessary medication both by the public and by the profession in the matter of vitamin preparations particularly polyvitamin capsules In the absence of suitable simple techniques for assaying the needs of a given individual for the various vitamins only the physician s common sense and good judgment can be used as guidance

Minerals—Of especial importance in the mineral content of the diet are calcium phosphorus and iron In planning a diabetic diet one must keep in mind accepted standards with regard to calcium and phosphorus The daily requirement for calcium for adults is stated to be 0 8 gram and for growing children 1 0 gram Since the important sources of calcium and phosphorus are dairy products including milk cream cheese and eggs the diabetic diet should be so arranged as to include these foods in adequate amounts This is important to keep in mind since in the pre insulin days rarely was enough milk given because of its carbohydrate content The growing diabetic child needs milk just as does the non diabetic and the diet should be arranged accordingly In Table X is listed the calcium content of some of the commoner foods In calculating diets one may keep in mind that 0 1 grams of calcium is supplied by each of the following milk 83 grams (approximately 3 ounces) light (20 per cent) cream 104 grams (approximately 3½ ounces) American cheese 11 grams (approximately 1/3 ounce) and three eggs In those patients placed on low calorie diets for weight reduction one must reduce or eliminate cream cheese and whole milk in order to keep the fat content of the diet low in such patients skimmed milk should be prescribed so that the calcium and phosphorus content of the diet will not suffer

It is a safe general rule that if the diet is adequate in calcium it will be adequate also in phosphorus since the two accompany each other In patients with osteoporosis pregnancy lactation or in those who for one reason or another are not able to take foods containing lime salts it may be necessary to prescribe such in the form of calcium lactate calcium gluconate dicalcium phosphate or calcium glycerophosphate

It is not uncommon to find in middle aged or elderly diabetics hypochromic anemia of slight or moderate degree Often with these

patients dietary iron must be supplemented by appropriate amounts of iron given preferably as a ferrous salt such as ferrous sulfate

Alcohol—The patient with diabetes does well to avoid alcohol entirely Although alcohol furnishes 7 calories per gram it is far from being a complete or desirable food Beverages which contain relatively small percentages of alcohol such as beer, ale and wines usually contain appreciable amounts of carbohydrate and are not well tolerated by the diabetic Thus, since beer contains about 5 per cent carbohydrate, a twelve ounce bottle (360 c c) will furnish 18 grams of carbohydrate which is as much or slightly more than that furnished by a slice (30 grams) of bread The carbohydrate content of sweet wines varies from the usual 5 or 6 per cent to as much as 20 per cent and that of cordials may run over 30 per cent Distilled liquors such as whiskey,

TABLE X

CALCIUM CONTENT OF COMMON FOODS

(average servings 30 grams = approximately 1 ounce)

	Weight gm	*Household Measure*	*Calcium gm*
Milk	40	½ pint	88
Cream 0 per cent	30	tablespoons	029
Ice cream	100	2 heaping tbsp	150
Egg	50	1	.034
Cheese American	30	1¹ × 1 × 1 in	279
Cheese cream	30	2 tablespoons	105
Cheese cottage	30	2 tablespoons	0 4
Meat cooked	100	3½ ounces	.016
Fish cooked	100	3½ ounces	.0 3
Fruits	100	small serving	.00, .049
Vegetables	100	¹ cup	.004 123
Nuts	30	1 ounce	.0 5
Breads and cereals (dry weight)			
White refined	30	1 slice or one serving	.006
Whole grain	30	1 slice or one serving	.015

brandy rum and gin contain from 20 to 50 per cent alcohol but furnish no carbohydrate (except that sugar is sometimes added to brandy) However hard liquors should be avoided by the diabetic also because of the danger of an individual with one chronic disease acquiring a second alcoholism Furthermore in both diabetes and chronic alcoholism peripheral neuritis is not an infrequent complication due in alcoholism at least, to vitamin B deficiency, and it is unwise to allow the patient to become a possible prey to this distressing complica

tion A third consideration is the fact that with patients taking insulin a hypoglycemic attack in one who has had only a small amount of alcohol may produce symptoms and signs difficult for the police and other non medical authorities to distinguish from those of acute alcoholism

Special Foods—In the pre insulin days when the amount of carbohydrate had to be kept extremely low it was common to use special foods such as gluten bread and bran biscuits Such special foods at that time had a definite place but now that insulin makes possible the taking of a more liberal diet there is no advantage to be gained in the use of special foods Gluten and other special breads are not preferable to ordinary breads since although they do contain less carbohydrate they contain more protein which after it is metabolized yields carbohydrate in the body Most special foods are more expensive and less palatable than regular foods An exception to the above statements may be made in the case of water packed fruits usually obtainable at larger grocery stores and markets which provide fruit with natural carbohydrate content at all seasons of the year A second exception may be made to satisfy the craving of diabetic children for candy gum and soft drinks by allowing occasionally preparations made without sugar

In the prescribing or granting approval for the use of special 'diabetic' foods the physician should take pains to see that the food actually contains no more carbohydrate than is claimed If personal analyses are not possible the best policy is to use foods only from reputable manufacturers

Diet for Days of Acute Illness—During days of minor illness and in the few days following a surgical operation or recovery from acidosis it is necessary to modify the regular diet If no food by mouth is allowed then 000 to 3 000 c c of 5 per cent glucose either in water or in normal salt solution may be given intravenously each 4 hours If fluids can be tolerated orally then ginger ale orange juice and other fruit juices tea with sugar clear soup and broths may be given at intervals during the waking part of the day so that a total at the very least of 100 grams and preferably 150 grams of carbohydrate per 24 hours are provided If soft solid food can be tolerated by the patient then a diet similar to that shown in Table XI may be prescribed

Special Lunches—Both in the hospital and at home many patients prefer to take a meal at noon and evening which are of the same general type although varying as to the specific foods served However with

patients dietary iron must be supplemented by appropriate amounts of iron given preferably as a ferrous salt such as ferrous sulfate

Alcohol—The patient with diabetes does well to avoid alcohol entirely Although alcohol furnishes 7 calories per gram it is far from being a complete or desirable food Beverages which contain relatively small percentages of alcohol such as beer, ale and wines usually contain appreciable amounts of carbohydrate and are not well tolerated by the diabetic Thus, since beer contains about 5 per cent carbohydrate a twelve ounce bottle (360 c c) will furnish 18 grams of carbohydrate which is as much or slightly more than that furnished by a slice (30 grams) of bread The carbohydrate content of sweet wines varies from the usual 5 or 6 per cent to as much as 20 per cent and that of cordials may run over 30 per cent Distilled liquors such as whiskey,

TABLE X

CALCIUM CONTENT OF COMMON FOODS

(average servings 30 grams = approximately 1 ounce)

	Weight gm	Household Measure	Calcium gm
Milk	40	½ pint	88
Cream 0 per cent	30	tablespoons	.0 9
Ice cream	100	heaping tbsp	150
Egg	50	1	.034
Cheese American	30	1 ½ × 1 × 1 in	2,9
Cheese cream	30	tablespoons	105
Cheese cottage	30	2 tablespoons	.0 4
Meat cooked	100	3½ ounces	.016
Fish cooked	100	3½ ounces	.0 3
Fruits	100	small serving	.007 .049
Vegetables	100	½ cup	.004 1 3
Nuts	30	1 ounce	.0 5
Breads and cereals (dry weight)			
White refined	30	1 slice or one serving	.006
Whole grain	30	1 slice or one serving	.015

brandy, rum and gin contain from _0 to 50 per cent alcohol but furnish no carbohydrate (except that sugar is sometimes added to brandy) However, hard liquors should be avoided by the diabetic also because of the danger of an individual with one chronic disease acquiring a second alcoholism Furthermore in both diabetes and chronic alcoholism peripheral neuritis is not an infrequent complication due in alcoholism at least, to vitamin B deficiency and it is unwise to allow the patient to become a possible prey to this distressing complica

TABLE VII

SUGGESTIONS FOR LUNCHEONS CONTAINING APPROXIMATELY 60 GM. OF CARBOHYDRATE

Food	*Household Measure*	*Weight Gm*	*Carbohydrate gm*	*Protein Gm*	*Fat Gm*
I					
Bread	2 slices	60	36	6	0
Meat	med. serving	75	0	20	13
Lettuce	as desired	—	—	—	—
Butter	1 square	10	0	0	8
Milk	½ pint	40	1	8	8
Orange	1 medium	150	15	0	0
Total			63	34	29
II					
Bread	2 slices	60	36	6	0
American Cheese	1 ounces	45	0	12	16
Lettuce	as desired	—	—	—	—
Egg	1	50	0	6	6
Milk	pint	40	12	8	8
Banana	1 small	75	15	0	0
Total			63	3	30
III					
Bread	2 slices	60	36	6	0
Choice of filling					
Crab meat, tuna, salmon	ounces	75	0	0	13
Lettuce	as desired	—	—	—	—
Mayonnaise	1 tablespoon	15	0	0	12
Milk	½ pint	40	12	8	8
Apple	1 small	105	15	0	0
Total			63	34	33

Substitutions and modifications may be made as indicated

Insulin

Using modern diets furnishing 150 to 00 grams of carbohydrate a day, approximately 75 to 80 per cent of diabetic patients will benefit from the use of insulin. The individual physician dealing with a single patient often has difficulty in persuading him to obtain the benefit of insulin. The patient dislikes the thought of making the injections and fears that if he starts the use of insulin he will be forming a habit that will remain with him throughout life. In overcoming this natural hesitancy on the part of the patient the physician should adopt the

others and particularly with school children and workers who are away from home at noon, it is imperative that special lunches be planned These should be simple in type and easily obtainable in any restaurant if not prepared at home In general such lunches consist of an ordinary meat or cheese sandwich, a piece of fresh fruit and eight ounces of milk In Table XII are given samples of such lunches these are offered only as suggestions and may be modified to suit individual needs

TABLE XI

EXAMPLE OF A CONCENTRATED DIET FOR A DAY OF MINOR ILLNESS

	Household Measure	*Weight gm*	*Carbohydrate*	*Protein*	*Fat*	*Calories*
Breakfast						
Orange Juice	ounces	100	10	0	0	40
Egg	1	50	0	6	6	78
Bread	1 slice	30	18	3	0	84
Butter	1 teasp	5	0	0	4	36
Milk	6 ounces	180	9	6	6	114
Mid morning						
Pineapple Juice	ounces	70	10	0	0	40
Lunch						
Oatmeal (cooked)	small serving	1 0	10	3	1	61
Milk	6 ounces	180	9	6	6	114
Cream o per cent	ounces	60	2		1	1 4
Bread	1 slice	30	18	3	0	84
Butter	1 teasp	5	0	0	4	36
Orange Juice	3 ounces	100	10	0	0	40
Mid afternoon						
Milk	6 ounce	180	9	6	6	114
Supper						
Egg	1	50	0	6	6	78
Bread	1 slice	30	18	3	0	84
Butter	1 teasp	5	0	0	4	36
Milk	6 ounces	180	9	6	6	114
Orange Juice	3 ounces	120	10	0	0	40
8 – 10 p.m						
Milk	6 ounces	180	9	6	6	114
	Total		151	56	60	1438

Note Substitutions may be made according to principles previously outlined Bread may ge given as toast in the amounts stated above crackers or other carbohydrate-containing food may be substituted for it in whole or in part

diabetes Whereas regular and crystalline insulin are clear solutions with a pH of about 3 0 3 5 protamine zinc insulin is a suspension with a pH of 7 0

(4) Globin (zinc) insulin[41] introduced to the American market in 194 represents the results of attempts to develop an insulin with action intermediate between that of unmodified (regular or crystalline) and protamine zinc insulin In this preparation another simple protein globin is combined with insulin and tiny amounts of zinc are added It is a clear solution which has a total length of action of 18 to 24 hours Whereas hypoglycemic attacks from unmodified insulin are most apt to come three or four hours after a given dose and those from protamine zinc insulin in 1 to 24 hours reactions due to globin insulin most often come about 8 or 9 hours after the dose has been taken or in the usual patient in the middle of the afternoon Globin insulin is stated to have the advantage of producing fewer allergic effects but one does see occasionally persons who are allergic to globin insulin as well as to other types Although many patients with mild or moderate diabetes can be controlled successfully with globin insulin it possesses few or no advantages over protamine zinc insulin or a combination of the latter type with unmodified insulin Its greatest disadvantage is that its length of action may be somewhat less than 4 hours so that in patients with severe diabetes there may be little or none of the overlapping effect which is such a valuable attribute of the longer lasting protamine zinc insulin

(5) NPH Insulin Many modifications of insulin are possible for the chemist and it is only those preparations which have seemed most promising that have been admitted to the market Others such as histone zinc insulin and soluble protamine zinc insulin[6] have been used with sizable groups of patients on an investigative basis but have been discarded as possessing no important advantages *NPH insulin*, a specially modified protamine insulin was placed on sale on October 16 1950 Like the globin variety it is an intermediate insulin However its duration of action is somewhat longer than that of globin insulin so that even in patients with severe diabetes its effect extends over 4 hours and usually 6 to 30 hours Like the NP 0 insulin used on an investigational basis by MacBryde and Reiss[66] it has only 0 5 mgm of protamine per 100 units of insulin whereas protamine zinc insulin contains 1 25 mgm per 100 units

The basis for the designation of this preparation as NPH insulin is as follows N refers to the neutral reaction of the product P refers

attitude that one should not try to avoid insulin if at all possible but to obtain its benefit whenever indicated If on a diet, which is necessary for the patient to maintain normal weight and strength the urine is not sugar-free or nearly so and blood sugar values are not at a satisfactory level then insulin should be prescribed unhesitatingly and very insistently

Treatment with insulin may be initiated in the office, the out patient clinic or the hospital Wherever it is done the patient must receive personal instruction in the use of the needle and syringe Except in the very elderly or the very young or in those in whom blindness or other physical infirmities prevent it one must insist that the patient be self-sufficient and give his own insulin

Types of Market Insulin —In the United States, there are at present five types of insulin commercially available

(1) Regular or plain insulin, the insulin of Banting and Best This type has a prompt effect and a duration of action of only five or six hours

(2) Crystalline insulin (solution of zinc insulin crystals) This type of insulin was placed on the market in the United States in 1938 Its action is so nearly like that of regular insulin as to be indistinguishable clinically, its length of action may be an hour or so longer[61] It has one possible advantage in that it is a more highly purified preparation than regular insulin but present day preparations of the latter type are of such high grade purity that this is of little consequence

(3) Protamine zinc insulin admitted to the market in the United States in 1937 Ever since the discovery of insulin the need had been felt for a preparation with slower effect of greater duration It had become evident early that in patients with severe diabetes 3 or 4 injections were necessary in 24 hours in order to control diabetes and even then it was difficult or impossible to control the blood sugar for most of the day and particularly in the period from midnight until morning Many attempts were made to develop an insulin with prolonged effect but most of the investigations were not as successful as those of Hagedorn[6] who combined insulin with a simple protein protamine This original preparation had an effect over about 12 hours of time later Scott and Fisher[63] showed that by the addition of a tiny amount of zinc the action of the preparation now known as protamine zinc insulin extended for 24 to 48 hours With protamine zinc insulin the control of diabetes became possible to an extent never before realized It has been of particular benefit to growing children with severe

control of the diabetic condition is possible by giving the two types of insulin separately However insulin mixtures have been and are being used extensively in various clinics over the country by physicians who report good results and continue to be enthusiastic about them In the adjustment of dosage in a given patient one increases or decreases the amount of protamine zinc insulin according to the urine and blood tests before breakfast One increases or decreases the amount of crystalline insulin included in the mixture by the outcome of urine and blood tests just before the noon meal The technique of making mixtures in the syringe has been described by Peck[6] Important points are that the crystalline insulin should be drawn into the syringe first and that a small quantity of air should be admitted to the vials before attempting withdrawal of the insulin

Beginning of Treatment with Insulin —When a patient is seen for the first time in the office or hospital it is often possible to predict whether or not insulin will be necessary One knows from experience that once the diagnosis of diabetes has been made almost 100 per cent of children and a high percentage of adolescents and young adults will require insulin On the other hand with many obese middle aged persons who have not previously restricted their diet it is possible to clear up glycosuria and to bring the blood sugar to a satisfactory level by restriction of diet and consequent reduction in body weight Indeed so great a metabolic change may be produced by correcting the obesity of certain patients that Newburgh[6] has questioned as to whether the diagnosis of true diabetes is warranted in these individuals The point is debatable but experience suggests that it is far safer to classify and treat such patients as diabetic throughout life

With patients not acutely ill and with whom time is available it is reasonable at the first visit to outline a restricted diet to teach the patient how to test the urine for sugar and to ask him to return a week later with a record of results of urine tests for sugar done before meals and at bedtime Then usually it will be obvious whether or not insulin is necessary The starting dose of protamine zinc insulin may well be 10 or 12 units daily before breakfast This dose then is increased gradually 2 to 4 units at a time until the urine tests before breakfast become free from sugar If at this point despite sugar free tests before breakfast significant glycosuria occurs during the day then one prescribes a small dose of unmodified (regular or crystalline) insulin to be taken daily in the morning before breakfast by separate injection Such a starting dose may well be 6 to 8 units The dose of

to the protamine content H refers to Dr H C Hagedorn of Copenhagen Denmark in whose laboratory this modification of insulin was prepared[67] Its advantages are (1) Since its duration of effect is shorter than that of protamine zinc insulin it possesses a quicker action, and accordingly it may be used in a single injection in many patients instead of giving two injections of the crystalline and protamine types ( ) Because of its relatively small protamine content and its predominantly crystalline characteristics, crystalline or regular insulin may be added to it in the syringe with preservation of most of the rapid action of the added insulin Thus, by one means or another, patients taking NPH insulin have the convenience of only a single injection daily Its activity roughly approximates that of the 2 1 mixture of crystalline and protamine zinc insulin

Insulin Mixtures—In recent years much work has been carried out with mixtures of regular (or crystalline) and protamine zinc insulin particularly by Peel[6] and Colwell[68] Mixtures may be made either in the syringe or in a bottle However, in using insulin mixtures the matter is considerably more complicated than simply mixing in the syringe the doses customarily taken separately This arises from the fact that market protamine zinc insulin contains for purposes of stability an excess of protamine To satisfy this excess one must add to a given number of units of protamine zinc insulin approximately the same number of units of unmodified insulin before the binding power of the excess protamine is used up Thus if one adds 20 units of crystalline or regular insulin to 20 units of protamine zinc insulin, it is roughly true that one will secure the effect of about 40 units of protamine zinc insulin Therefore in preparing insulin mixtures the amount of unmodified insulin must exceed that of protamine zinc insulin before any appreciable rapid effect may be expected The proportion found to be most generally useful is that of two parts of unmodified to one part of protamine zinc insulin Colwell believes that 85 per cent of diabetic patients requiring both types of insulin can be regulated satisfactorily on a single dose of the - 1 mixture Others favor a 3 2 mixture

The outstanding advantage of insulin mixtures is the avoidance of one injection Disadvantages are (a) less flexibility in the adjustment of the dose of the two types of insulin from time to time if mixtures in a vial are used and (b) technical difficulties encountered by the patient in accurately measuring doses of two types of insulin in one syringe The writer believes that with most patients better and more continuous

blood sugar to rise between midnight and morning In the past some have attempted to overcome this by taking a dose of insulin at 1 or 2 a m but this is inconvenient, disturbing to sleep and still does not provide a continuous basic influence on the blood sugar such as protamine zinc insulin does

In the early days of the use of protamine zinc insulin it was often stated that patients had more hypoglycemic attacks with this type of insulin than with unmodified insulin This need not be so if care is taken in the regulation of the insulin dose The dose of protamine zinc insulin must never be increased beyond that point at which a sugar free urine and normal or near normal blood sugar values are obtained 24 hours after the last injection of this type of insulin As has already been brought out the urine and blood tests before breakfast may be satisfactory and yet much glycosuria be noted during the course of the day In this situation any additional insulin given to clear up the glycosuria must not be of the protamine zinc type but of the regular or crystalline variety given preferably as an accompanying dose in the morning before breakfast by separate injection

The time of day at which protamine zinc insulin is given is not of great importance as long as it is given at the same time each day Although there is no reason why protamine zinc insulin cannot be taken daily before the noon or evening meals in actual practice it works out best with most patients to have it taken in the morning before breakfast

Treatment with NPH Insulin — Extensive use of NPH insulin or its forerunners (NPC 50 and NPH50) has been made by the writer and associates[1,9] since early in 1948 It has proved so valuable that at the present time most new patients are being started on it In achieving adjustment the procedure is essentially the same as that outlined above for protamine zinc insulin In many patients proper control may be obtained by a single injection of NPH insulin daily In those in whom gradual increase in dosage has brought about control to the point at which urine and blood tests before breakfast are satisfactory and yet significant hyperglycemia and glycosuria still are present just before the noon meal one adds a small dose say 4 to 6 units of crystalline insulin to the NPH variety in the syringe The mixture is made in the same manner as the mixture of crystalline and protamine zinc insulin drawing the crystalline insulin into the syringe first The dose of added crystalline insulin is adjusted at that level which will yield satisfactory urine and blood tests just before the noon meal

unmodified insulin then is increased 2 units at a time until the urine tests before the noon meal are uniformly good, varying between light green and blue with Benedict's test. When the point is reached at which the urine tests before breakfast and before the noon meal are uniformly good, in the average case the excretion of sugar during the rest of the 24 hours will be negligible or small, and no additional insulin need be prescribed before the noon or evening meals. Occasionally, however, with severe diabetes a small dose of unmodified insulin may be necessary before the evening meal. Often to avoid this shifting of food from the later to the earlier part of the day may overcome late afternoon and evening glycosuria.

Almost all patients can be taught to make minor variations in their insulin dosage at home. They are instructed that the urine test before breakfast is the best index of the effect of protamine zinc insulin and that the urine test before the noon meal is the best index of the effect of unmodified insulin. They are taught to make increases or decreases, 2 units at a time in either or both types of insulin allowing at least 2 or 3 days between changes. One discourages frequent changes or undue tampering with the insulin dosage but the intelligent patient with the above facts in mind can often bring about good regulation even in the midst of changing insulin requirements.

The above process of initial regulation may require 3 or more weeks with an office patient. With patients in the hospital it is possible to proceed much more rapidly and the weeks are telescoped almost into days. Rarely is it necessary for a patient with uncomplicated diabetes to stay longer than a week in the hospital for preliminary regulation. To be sure, usually further minor adjustments of diet and insulin dosage will be required during succeeding weeks but during the 5, 7 or 10 days spent in the hospital much can be accomplished. Not infrequently insulin may be used for short periods to hasten regulation and then gradually given up to allow control by restriction of diet alone.

Rarely will it be desirable to use unmodified insulin to the exclusion of protamine zinc insulin. If unmodified insulin is used alone then from 1 to 4 doses a day are necessary. If one dose is given this is before breakfast; if two, before breakfast and supper; if three, an additional dose at bedtime is given and with patients with severe diabetes a fourth dose before the noon meal may be required. It must be emphasized that in the patient with severe diabetes even the above schedule will not care adequately for the marked tendency for the

If urine test is	Red or Orange	Yellow or Yellow green	Green or Blue
Give regular or crystalline insulin units	10	6	0

The actual number of units prescribed in the above fashion will vary depending upon the patient and situation at hand A second plan used by some but not preferred by the writer is to discontinue temporarily protamine zinc insulin and to obtain tests for the urine for sugar at 3 or 4 hour intervals throughout all or most of the 24 hours giving unmodified insulin according to the tests The orders left might read somewhat as follows adjusting the size of the doses to the predicted needs of the patient

If urine test is	Red or Orange	Yellow	Yellow green	Green or Blue
Give regular or crystalline insulin units	16	12	8	0

During the period of regulation of poorly controlled diabetes particularly if the patient is in the hospital time may be saved by use of regular or crystalline insulin before the noon and evening meals given in doses graduated to conform to urine tests at those times However it must be stated emphatically that the aim of a period of regulation in the hospital should be establishment of a dose of (a) protamine zinc or NPH insulin alone or of (b) protamine zinc or NPH insulin plus regular or crystalline insulin which will provide control of diabetes without the giving of insulin during the rest of the day Adjustments in this dose will be necessary from time to time but should not be made daily on the basis of single tests

Insulin Lipodystrophy —Lipodystrophies due to insulin include both atrophy and hypertrophy of subcutaneous fat *Atrophies* are seen far more commonly the name refers to the disappearance of subcutaneous fat which occurs in some patients at the site of insulin injections It is commonly noted only after insulin has been taken for about 6 months although since the onset usually is gradual and insidious it is difficult to establish definitely the period of time required for development Rarely insulin atrophies have been described as occurring at some distance from any area known to have received insulin but such instances are

Patients already on a single dose of protamine zinc insulin usually may be shifted to a similar dose of NPH insulin, although there would appear no reason for doing this, if the diabetic condition is well controlled on the program already in effect It is with patients taking separate injections of crystalline and protamine zinc insulin that the greatest advantage lies in shifting to the NPH type If the dose of crystalline insulin is relatively small, say one fourth to one third that of the protamine zinc variety usually one may shift to a single dose of NPH insulin giving the sum of the doses of the other two types In those patients in whom the ratio of crystalline to protamine zinc is 1 or greater often a single dose of NPH insulin alone will not suffice In such patients if one attempts to give the entire amount of insulin in the form of the NPH variety, one may produce hypoglycemic reactions in the mid afternoon evening and night In the attempt to control hypoglycemia the use of mid afternoon lunches and the shifting of foods in general toward the latter part of the day may be effective in some instances but often one is forced to reduce the dose of NPH insulin and add a small dose of crystalline insulin to it in the syringe In general with patients taking NPH insulin a mid morning lunch is not necessary but provision should be made for a mid afternoon lunch with 10 to 15 grams of carbohydrate and a bedtime lunch with 15 to 20 grams of carbohydrate

Administration of Insulin at Frequent Intervals—There are times when it becomes necessary to administer insulin more frequently than outlined above When this is done regular or crystalline insulin should be used rather than protamine zinc insulin in order to avoid a cumulative effect of the latter Situations demanding frequent administration of insulin include (a) during treatment of diabetic acidosis and coma (b) following surgical operations (c) during acute infections when the insulin requirement is temporarily increased and (d) during the initial adjustment period

Recommendations regarding the use of insulin during the treatment of acidosis and coma will be given in detail later in a section devoted to that complication Following surgical operations or during acute infections one may adopt either of two general plans The preferred method is to continue the basic dose of protamine zinc insulin with or without unmodified insulin in the morning before breakfast and to give unmodified insulin in the late forenoon and late afternoon according to the results of urine tests for sugar obtained at those times Orders may be left to give insulin as follows

The treatment of insulin atrophies is unsatisfactory since the cause is unknown The following suggestions however have proved worth while

(1) From the outset of treatment patients should establish a rule of scattering injections over large areas of the body surface If the thighs are used for injections then imaginary maps should be used giving injections in parallel columns down the thighs so that no one area 3 to 4 cm in diameter receives insulin oftener than once a month This will have the added effect of keeping the skin soft and pliable



FIG 5 Atrophy of subcutaneous fat due to insulin

A Back of thigh of N R female aged 35 years with diabetes of 4 years duration

B Upper arm of N M, female aged 59 years with diabetes of 2[illegible] years duration

Note in both instances the extensive loss of subcutaneous fat exposing the outlines of underlying muscles and veins Atrophies were first noted about 6 to 8 months after beginning to use insulin in a given area

(2) *The use of high strength insulin (U 80) to keep to a minimum* the volume of fluid injected

(3) Care in expelling the last traces of alcohol from needle and syringe prior to loading with insulin

not well documented and cannot be considered as proved. The condition occurs almost exclusively in children, adolescents and women and only uncommonly in adult males. A person, who is susceptible to atrophies is likely to develop them wherever injections are given, in the arms, thighs, flanks, abdominal wall and over the buttocks. Insulin atrophies are painless and have no importance other than cosmetic. Biopsies through regions of atrophies for histological and chemical analyses have shown that the lesion consists solely of the disappearance of neutral fat without damage to any important structures such as muscles, nerves or blood vessels. There is no suggestion of infection or inflammatory disease. If injections of insulin are discontinued in an atrophied area there will, in most cases and particularly in children, take place slowly over months of time complete or partial restoration of subcutaneous fat. The characteristic appearance of marked insulin atrophies is shown in Fig. 5.

The mechanism by which insulin atrophies occur remains unknown. As possible causes have been suggested the mechanical injury due to repeated injections, the tricresol formerly used as a preservative in market insulin, low grade inflammation, contamination of insulin with alcohol used in sterilizing the needle and syringe and local oxidation of carbohydrate which in turn causes an active combustion of local fat[70]. None of these possible explanations has been shown to be valid. The melting away of the subcutaneous fat certainly suggests the action of a lipolytic agent such as tissue lipase. Whether in some individuals the injection of insulin sets up conditions favorable for the action of such is impossible to say. That the disorder may be related in some way to the activity of sex hormones is suggested by its infrequent occurrence in adult males. However, Oestreicher[71] found that the administration of oestradiol dipropionate had no effect upon the amount of fat at the sites of injection of insulin in either diabetic or non diabetic rats.

Atrophies are seen almost exclusively in those patients who inject insulin time after time and day after day into a single or a few small areas. They represent presumably ingrowth of fibrous tissue in response to the repeated trauma of injections and therefore are preventable. Other than their disfiguring nature they have the importance that insulin given into such scarred areas is not absorbed as rapidly or as efficiently as when deposited beneath normal skin. Furthermore, such areas appear to have a local lowered resistance to infection and may become the sites of abscesses following an unclean injection which the body normally could withstand.

The treatment of insulin atrophies is unsatisfactory since the cause is unknown The following suggestions however, have proved worth while

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(2) The use of high strength insulin (U 80) to keep to a minimum the volume of fluid injected

(3) Care in expelling the last traces of alcohol from needle and syringe prior to loading with insulin

(4) Care to deposit the insulin well under the skin

(5) In susceptible people the best advice is to avoid those areas of the body which may be exposed to public view and to use the skin of the abdominal wall, flanks and above the buttocks It is best to advise discontinuance of injections in an area where atrophies have appeared to allow possible restitution of subcutaneous fat Some clinicians as Collens, Boas Zilinsky and Grewald[120] have reported on the contrary that the giving of insulin into the depths of atrophied areas would result in restitution of subcutaneous fat However, in the writer s experience this is by no means always so although the procedure has some theoretical background (Renold, Marble and Fawcett[121]) There is no evidence to indicate that the rubbing of ointments into the skin hastens restoration of fat

Insulin fat hypertrophy is encountered about as commonly as insulin atrophy, especially in children However, it attracts much less attention and concern In this condition there is a localized increase in the amount of subcutaneous fat without evidence of inflammation

Allergy to Insulin—Insulin is a protein of animal origin and modified preparations contain other proteins such as protamine and globin It is not surprising, therefore, that a large percentage of patients exhibit, to a greater or less degree sensitivity to insulin in the allergic sense These usually take the form of untoward skin responses at the site of injections, although uncommonly there may occur generalized urticarial and rarely, definite anaphylactic reactions

Local skin responses are common in patients at the beginning of treatment particularly with the use of protamine zinc insulin Many patients develop within 30 minutes to a few hours swelling, redness and tenderness at the site of injections At times one or more urticarial wheals may be present The patient complains of pain and possibly itching Treatment consists of reassurance and the prediction that within a few or several days or at most a few weeks the untoward responses will cease gradually Local discomfort may be alleviated somewhat by the use of cold compresses Helpful in some cases is the giving of an antihistaminic agent such a benadryl or pyribenzamine in dosage of 50 mgm or more three or four times a day Generalized urticarial reactions are seen most frequently in patients who have taken insulin in the past and have resumed it after a period of weeks months or years during which no insulin has been taken In such patients, fortunately few desensitization may prove to be quite a problem Various methods have been used in treatment

(1) Occasionally but not often it may be found helpful to change the brand of insulin used Success in certain few patients probably depends upon the fact that the insulin of certain manufacturers is made from beef pancreases alone whereas others use a mixture of beef and pork pancreases

(2) Low carbohydrate diets have been advocated for use in certain patients in order to lessen the need for insulin Rarely is this justifiable and in the present day it is with hesitancy that one prescribes diets with less than 150 grams of carbohydrate a day One must always keep in mind that infection in the diabetic patient may suddenly and markedly increase the insulin requirement even in the mild case

(3) *Desensitization* Although some have reported good results with non specific desensitization with histamine most clinicians have found it best to desensitize the patient with repeated injections of insulin starting with a very small dose and increasing the amount gradually *Rapid desensitization over a period of 24 hours may at times be* possible but in the usual case a slower procedure is advisable One gives initially 0 001 units of insulin subcutaneously using either regular or crystalline insulin If no appreciable local response follows the dose is approximately doubled with each succeeding dose When no emergency exists 4 doses may be given conveniently each day i e before each meal and at bedtime To make the first preparation used one places 4 units of crystalline insulin in 40 c c of normal salt solution one then dilutes 1 c c of this solution with 9 c c of normal salt solution Thus the final preparation contains 0 001 unit of insulin in 0 1 c c of solution The insulin dose might be somewhat as follows first day 0 001 0 002 0 004 0 008 second day 0 01 0 02 0 04 0 08 third day 0 2 0 5 1 0 o If at any point in the gradual increase of insulin dosage significant untoward effects follow an injection then one returns temporarily to the next lower dose and begins the ascent in dosage again When the patient is able to tolerate as much as 2 units at a single injection then doses are given only before meals increasing the number of units gradually to the level necessary for the patient at hand Shift to protamine zinc insulin then should be made gradually starting with a trial dose of only 1 or 2 units

As stated above the use of an antihistaminic agent may facilitate greatly the process of desensitization and in less sensitive persons may suffice alone In cases of marked allergy to insulin it may be advantageous to mix a solution of an antihistaminic agent with insulin and inject the two together

Exercise

Of importance in the treatment of diabetes along with diet and insulin is physical activity It is a matter of everyday experience that exercise aids in carbohydrate utilization and intensifies the action of insulin on the blood sugar It is a common finding that hypoglycemic attacks may follow exercise of unusual nature particularly in the person with well regulated diabetes The value of exercise in lowering the insulin requirement is seen strikingly in children in summer camps Here patients are able to take more food and yet have the diabetic condition better controlled with a smaller dose of insulin than has been the case at home when particularly due to school sessions opportunities for regular exercise have been less

It follows from the above that all patients should be encouraged to take exercise regularly Most diabetic patients are in middle life or beyond and for them walking is often the best form of physical activity Patients engaged in sedentary occupations must be impressed with the fact that moderate exercise regularly taken is far better for them than strenuous exercise irregularly taken It goes without saying that in one's advice regarding exercise due regard must be taken of complicating conditions such as heart disease or other infirmities

In the hospital patients should be allowed street clothes and to be up and around They should be encouraged to take exercise out of doors at intervals during the day and thus approximate to some degree the amount of activity in which they engage at home Bed patients need not be wholly inactive and complication conditions permitting should exercise the arms with dumb bells or other appliances and with Buerger exercises for the lower extremities

Treatment of Diabetes in Childhood

In the treatment of diabetes in children and in adolescents the same general principles hold as with adults However juvenile diabetes has certain characteristics which must be taken into account, if treatment is to be successful In the first place diabetes in children usually is severe and the blood sugar is labile responding quickly on the one hand to food and on the other to insulin Consequently the first difficulty becomes that of striking a compromise so that the diabetic condition can be well controlled and yet frequent insulin reactions not

occur In the second place in the growing child one must be even more careful regarding the adequacy of the diet than with the adult The diet should provide truly adequate amounts of protein vitamins and minerals so as to insure normal growth and development In the third place the occurrence of diabetes in children poses certain psycho logical problems The child has even greater difficulty than the adult in adjusting himself to his disease and the limitation enforced on his freedom by virtue of it

Diagnosis

The diagnosis of diabetes in childhood is rarely a problem If the condition is present at all it exists usually in severe form so that prior to treatment glycosuria is marked and the blood sugar is high The onset of the disease is apt to occur more precipitously than in the adult and usually it is much easier to decide as to the approximate date of onset in children than in older patients Not infrequently dia betes has not been suspected until acidosis or coma occurs

Although one is accustomed to seeing sizeable groups of children with diabetes in large out patient departments and clinics and the problem of the future of these patients is a most important one actually diabetes under the age of 20 and particularly under the age of 15 is uncommon It is likely that no more than one child in ooo - 500 has diabetes It has been estimated that in the United States today there are about 13 000 diabetics under 15 years of age The series at the George F Baker Clinic included up to the end of 1949 873 patients in whom the onset occurred before 15 years of age of these - 381 or 8 per cent were known to be living as of January 1950 (only o of the entire group of 2 873 were untraced)

Diet

Prior to the discovery of insulin it was impossible to provide an adequate diet for a diabetic child and it was the rare child who lived longer than - years following onset of the disease With the discovery of insulin it became possible for the first time to provide a diet adequate in calories and essential elements so that growth and development could take place normally In estimating the number of calories re

quired White[9] suggests a simple and easily remembered rule, namely, to allow 1 000 calories a day for a child aged one year and to allow an additional 100 calories for each year until the completion of growth or until about age 13 in girls and about age 19 in boys. Thus the maximum diet for a girl would be about 2 200 calories and for a boy about 2 800 calories a day. Average caloric requirements are summarized in Table XIII. Excess calories must be avoided for girls after

TABLE XIII

AVERAGE DAILY CALORIC ALLOWANCE OF DIABETIC CHILDREN LISTED ACCORDING TO AGE

Age Years	*Boys Calories*	*Girls Calories*
1– 5	1000–1400	1000–1400
5–10	1400–1800	1400–1600
10–15	1800–2000	1600–1800
15–20	2000–2800	1800–2200

maturity in order to prevent adolescent obesity. Suitable dietary prescriptions arranged according to age are shown in Table XIV. Diets such as those just outlined are adequate and liberal and yet are by no means 'free'. The method followed and advocated by some of allowing patients to eat an unrestricted diet without regard to sweets, pastries and other carbohydrate foods is considered unwise. Every attempt should be made to control diabetes in children as well as possible, admitting that this is a difficult task.

TABLE XIV

DIET FORMULAE USEFUL IN CHILDHOOD AND ADOLESCENCE

Age Years	*Sex*	*Carbohydrate gm per day*	*Protein gm per day*	*Fat gm per day*	*Calories per day*
5	M or F	140	60	70	1430
10	M or F	160	70	80	1640
15	M or F	180	80	90	1850
20	F	200	90	100	2060
20	M	50	110	120	25 0

It is with growing children that special attention must be paid to the protein content of the diet. This will vary from approximately 1 gram per kilogram in adolescents to as high as 4 grams per kilogram per day in very young children. Care should be taken to provide at least 1 gram of calcium per day; this will be possible if at least 1 to 1½ pints of milk are included in the daily diet. To forestall vitamin deficiency, dietary supplements are necessary. Cod liver oil or fish liver oil concentrates should be given in standard dosage to cover requirements of vitamin A and D and sufficient citrous fruits and vegetables given so that the vitamin C intake will be adequate. Vitamin B deficiencies should be kept in mind and supplements given if necessary. However, if a normal amount of the protein allowance is taken in the form of meat, liver and eggs, and if vegetables are taken in the amounts usually prescribed in diabetic diets, no difficulties should be encountered in this regard.

The total calories included in the diets of diabetic children may be furnished as follows: by carbohydrate 40, by protein 20 and by fat 40 per cent. The physician may calculate roughly that the number of grams of carbohydrate furnished daily will be about 10 per cent of the figure for total calories; the number of grams of protein and of fat will be in each case approximately half the figure for the carbohydrate. Thus, if about 1,600 calories are to be allowed daily, the amount of carbohydrate prescribed might be 160 grams and the amount of protein and fat each 80 grams a day. It is in general unwise to prescribe diets calling for more than 250 grams of carbohydrate a day, because in order to provide such, one must include foods of concentrated carbohydrate content which are difficult for a diabetic to utilize. The carbohydrate of the day may be divided by giving ⅓ at each of the three main meals, or ⅕ at breakfast, ⅖ at lunch and ⅖ at supper. With juvenile patients better results are secured if food is distributed throughout the waking part of the day and the burden at any one time is lessened. Consequently, children will do well to have mid-morning, mid-afternoon and bedtime lunches, thereby reducing the amount of food at the three main meals.

The distribution of food between the three main meals and between-meal lunches depends upon the times of maximal physical exertion and the variety of insulin used. Thus with globin insulin a mid-afternoon lunch is imperative in order to avoid hypoglycemia at that time of day. With NPH insulin a mid-afternoon lunch containing 10 to 15 grams of carbohydrate and a bedtime lunch with 15 to 20 grams of carbohydrate are necessary.

Insulin

The character of diabetes in children is such that once the diagnosis of the condition is made treatment with insulin should be started and continued without interruption The diabetic child needs the benefit of a constant insulin effect in the body This is brought out well in the contrast between the condition of diabetic children before and after the introduction of protamine zinc insulin Prior to 1937, when protamine zinc insulin was made available, great difficulty was experienced in preventing the rise in blood sugar which took place in the average diabetic child from midnight to morning despite a bedtime dose of insulin Consequently even under otherwise good programs of treatment satisfactory control was achieved during not more and often considerably less than 18 of the 24 hours a day Under conditions of inadequate control such as this it was not uncommon to encounter complications such as dwarfism, hepatomegaly and retardation of bone and sex development[3] With the introduction of protamine zinc insulin control of diabetes for a larger part of the 24 hours became possible and complications such as those described are much less common However it must be freely admitted that with the insulin preparations available today it is usually not possible under ordinary conditions to achieve excellent control of diabetes over 20 years of time in patients with onset of the disease in childhood There is much evidence to suggest however that if this were possible the diabetic child would truly be converted into a normal person and would be free from the late complications of the disease chiefly vascular damage which now beset him

The insulin of choice in the diabetic child is protamine zinc or NPH (at the present time in the practice of the writer and associates, most children are receiving NPH insulin daily before breakfast either alone or with a small amount of crystalline insulin mixed in the syringe) insulin and the dose given should be that amount which will provide for a satisfactory blood sugar in the morning before breakfast, assuming that this type of insulin is given before breakfast once daily The diabetic child must almost invariably requires rapidly acting (regular or crystalline) insulin in addition to the slowly acting protamine zinc insulin variety This rapidly acting insulin is given by separate injection in the morning before breakfast at the same time as the protamine zinc insulin (see a previous page for a discussion of insulin mixtures) The dose given is that amount which will provide a satisfactory blood sugar just

before the noon meal Usually these two injections of insulin both before breakfast are adequate for satisfactory control Occasionally an additional dose of regular or crystalline insulin will be necessary before the noon meal or the evening meal In beginning insulin treatment with children one may keep in mind that the average diabetic child under the age of 5 will require roughly a total of 10 units a day from 5 to 10 years 20 units and from 10 to 15 years 30 units Minor adjustments are made according to pre meal tests of blood and urine As far as urine tests are concerned it should be pointed out that due to the tendency to greater fluctuation of the blood sugar in the child the test for urine sugar may be misleading unless the patient is asked to pass the urine and then 15 to o minutes later to pass a second specimen This second specimen will more nearly reflect the level of the blood sugar at the time

Children are particularly susceptible to insulin reactions because of the usual lability of the blood sugar and common sensitivity to insulin and the fact that with a child it is more difficult to secure uniformity in matters of diet and physical exercise Consequently when children are active physically reactions should be anticipated and avoided by the giving of extra food The treatment of reactions is the same as that outlined elsewhere for patients in general No child should have frequent severe attacks of hypoglycemia even though the avoidance of such may mean a definite compromise with the ideal aim of treatment which is perfect control of diabetes Long continued severe hypoglycemia may bring about irreversible changes in the central nervous system and are a definite hazard

Atrophy of subcutaneous fat due to insulin already discussed in some detail earlier occurs in 40 to 50 per cent of children (Marble and Renold[12])

The physician must be wary in the treatment of the young patient who comes with recently discovered diabetes Occasionally in such patients one sees such marked improvement following initial aggressive treatment with a restricted diet and insulin that one is tempted to discontinue insulin entirely Indeed at times it may seem as if the diabetic condition were cured Experience has shown however that within a few weeks to a few months the diabetes reasserts itself in its true form Consequently in all children with diabetes insulin should be given daily from the time of diagnosis even though for short periods only a token dose is necessary

Exercise

As with other patients physical activity benefits the diabetic child not only in promoting general health and muscular development but also in reducing the insulin requirement Children should be encouraged to exercise regularly and there is almost no sport in which they may not take part They must of course, learn to forestall reactions by taking between meal lunches

Summer Camps

A valuable adjunct to the treatment of diabetes in children are the summer camps of which a number (12 in 1950) have been established over the United States Commonly a child spends from 2 to 9 weeks in camp During this period his life and daily activity approach that of a child in the average summer camp in the country with the exception that weighed diets are provided insulin is given daily, and tests of the blood and urine for sugar are taken as would be done if the patient were in a well-run hospital Medical and nursing supervision is provided The summer camp program represents one of the most forward steps taken in the treatment of juvenile diabetes It affords an opportunity for annual study and appraisal under excellent conditions amid surroundings which make life enjoyable for the child himself By no means unimportant are the rest and freedom from worry which are afforded parents of the children during the camp period

Complications in Childhood

The complications most commonly seen in diabetic children are diabetic coma infections of various types retardation of growth and development and after 10 to 20 or more years of diabetes degenerative vascular disease including retinitis arteriosclerosis hypertension and nephritis Neuropathies are infrequent in juvenile diabetics except in cases of long duration Skin lesions include necrobiosis lipoidica diabeticorum xanthosis and xanthomata

Diabetic coma occurs with relatively greater frequency in the diabetic child than in the adult Annually approximately 40 per cent of patients admitted in diabetic coma to the George F Baker Clinic are

patients whose onset of diabetes was at the age of 15 years or under The rules of treatment of coma are the same as in the adult except that smaller doses of insulin are required Nevertheless care should be taken to give adequate amounts of insulin within the first 3 hours of treatment Barring complications fatal in themselves all children should recover unless they are brought for treatment in a near moribund condition after hours of unconsciousness Death from diabetic coma in a child is always due to negligence on the part of someone

Children with uncontrolled or poorly controlled diabetes are particularly susceptible to *infections* especially of the skin and urinary tract Furthermore tuberculosis of the lungs occurs more frequently in diabetic children than among children of comparable ages in the general population The guiding principles in management should be prevention and early treatment Non tuberculous infections are now much easier to control by means of sulfonamides and antibiotics As regard tuberculosis annual x rays of the chest should be carried out and if tuberculosis is discovered appropriate measures should be instituted recent work indicates the benefit in certain patients of streptomycin and in others of surgery carefully planned and executed

Mention has already been made of the fact that particularly prior to the introduction of protamine zinc insulin with its prolonged action retardation of growth and development was much more frequent than it is at the present time The child most susceptible to dwarfism is the one whose age at onset of diabetes was under 5 years The retarded diabetic child usually shows normal intelligence despite infantile proportions and immature behavior In dwarfed or retarded children enlargement of the liver is found not infrequently together with protuberant abdomen There is delay of bone development and retardation of sexual development Certain studies[8] indicate that there is an increase in the serum follicle stimulating hormone and a decrease in the excretion of 17 ketosteroids in the urine Treatment of the retarded patient consists in supplying a diet adequate in calories high in protein (approximately 2 grams per kilogram of body weight daily) and vitamin supplements Medication which has been found useful in certain patients has included thyroid extract anterior pituitary extract and sex hormones (testosterone to retarded boys and estrogens to retarded girls)

Reference has been made earlier to the high incidence of vascular disease in patients with diabetes of 10 or more years duration This is most easily demonstrable in patients with onset of diabetes in childhood

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Diabetic coma occurs with relatively greater frequency in the diabetic child than in the adult. Annually approximately 40 per cent of patients admitted in diabetic coma to the George F. Baker Clinic are

perhaps whole blood or blood plasma intravenously and by the use of ammonium chloride and mercurial diuretics to bring about marked loss of unwanted fluid from the body with great temporary improvement in the condition of the patient However as time goes on the condition recurs and therapeutic efforts become less and less successful Death takes place in uremia a few to several years after the onset of definite symptoms of nephritis Postmortem examination usually shows the kidney lesions to be of mixed type including those of intercapillary glomerulosclerosis

The course already summarized constitutes the real problem in the care of the juvenile diabetic today It is difficult to prevent the development of generalized vascular disease and once the process has begun treatment is unsatisfactory

Certain few patients whose diabetes has been meticulously controlled over 0 years of time have been found to be free from vascular complications or nearly so The experience with this small group lends great weight to the belief that the vascular complications are due to poorly controlled diabetes and that if it were possible to bring about perfect control such complications would occur to no greater extent than in non diabetic individuals Aims for the future must include (a) *as nearly perfect and continuous control of diabetes as can be brought* about by existing agents and (b) attempts to improve treatment including the development of varieties of insulin which will allow better control

Complications of Diabetes

In the period 1898 to 1914 the average diabetic died at the age of 44 5 years after an average duration of the disease of 4 9 years (experience of Joslin and associates[9]) From 1914 to 19 the average age death had risen to 46 7 years and the average duration of diabetes to 6 1 years However with the discovery of insulin and the ability to control the acute complications of diabetes a dramatic change occurred and remarkable lengthening of life became possible Thus in the period 1944 to 1949 the average age at death was 64 3 years 20 years greater than that in the first period mentioned above and the average duration of diabetes among these deceased patients was 14 4 years The life expectancy of the diabetic therefore now approaches that of the person in the general population of comparable age although as yet does not

In Table XV are given statistics regarding the incidence of certain vascular complications in erstwhile juvenile patients As nearly as one can reconstruct the course of events one of the earliest evidences of vascular disease is that of retinitis with fine deep retinal hemorrhages and waxy exudates This process may lead eventually to retinitis proliferans and partial or complete loss of vision Along with the development of retinal hemorrhages there occurs sclerosis of the retinal arteries and throughout the rest of the body arteriosclerosis becomes recognizable, particularly if one carries out routine x rays of the aorta (lateral views), pelvic arteries and arteries of the legs Then small amounts of albumin appear

TABLE XV

INCIDENCE OF VASCULAR DISEASE IN 200 PATIENTS AS RELATED TO DURATION OF DIABETES IN AGE (WHITE[4])

(Patients 15 0 years of age or under at onset of diabetes)

Duration of Diabetes Years	*Retinal Sclerosis Per Cent*	*Retinal Hemorrhage Per Cent*	*Calcified Arteries Per Cent*	*Nephritis Per Cent*
0– 9 9	[illegible]	3	3	1 5
10–14 9	10	10	7	5
15–19 9	50	45	40	30
0 or more	85	80	75	50
Age of Patient Years				
0 5–19 9	8		5	1
20– 9 9	60	50	50	30

in the urine and as years go by the tendency to albuminuria increases The blood pressure gradually rises over years of time and impairment of renal function becomes demonstrable by urea clearance tests or by phenolsulfonephthalein excretion Later elevation in the blood non protein nitrogen begins and may become chronic A lowering of the total serum protein occurs particularly in the albumin fraction With this a tendency to edema asserts itself which with further lowering of blood proteins becomes generalized, leading to anasarca By this time the blood pressure may be distinctly elevated cardiac hypertrophy may have occurred and at the time of renal failure concomitant heart failure may be present At this stage periods of nausea and vomiting are common When such an episode of acute illness occurs for the first few times it is usually possible by the use of a high protein, low sodium diet and

Diabetic coma represents the end result of uncontrolled diabetes in the acute sense just as arteriosclerotic complications represent the end result over a long period of time. In the pre-insulin days more than 60 per cent (actually 63.8 per cent of 3[illegible]7 deaths 1898 to 1914) of all deaths in diabetics were in coma[8]. This fact is apt to be lost sight of today by both physicians and patients because treatment seems so easy and at the moment complications may seem relatively remote. At the present time, thanks to insulin, deaths from diabetic coma are relatively uncommon. Of 651 deaths in diabetics from 1944 to 1949 only 1.9 per cent were in coma. In the pre-insulin days diabetic coma was the

TABLE XVI
DECLINE IN PERCENTAGE OF DEATHS DUE TO COMA
(10,6[illegible]3 fatal cases)

Period Years	Total Deaths Number	Deaths Due to Coma Number	Deaths Due to Coma Per Cent
1898–19[illegible]4	32[illegible]	[illegible]09	63.8
1914–19[illegible]	816	34	41.5
19[illegible]2–[illegible]6	4061	340	8.4
1937–1943	3151	98	3
1944–1949	99	43	1.9

Experience of Joslin and associates. Statistics compiled with the cooperation of the Statistical Bureau of the Metropolitan Life Insurance Company.

almost inevitable culmination of a diabetic life and it was the unusual diabetic child who lived longer than two years. Now diabetic children are living on and on although it must be admitted that after 15, [illegible]0 or [illegible]5 years of diabetes they are experiencing serious difficulties with degenerative vascular disease.

Despite this lowered incidence of diabetic coma it remains always a potential menace and hazard. Despite the fact that it is a preventable condition even today it occurs all too frequently. Furthermore despite more than [illegible]5 years of experience with insulin, inadequate doses often are administered and deaths result from poorly planned treatment.

Pathogenesis.—As has been discussed somewhat in detail in the section on Physiology, in the normal person fats are broken down in the liver to form the so-called acetone bodies, beta-hydroxybutyric and acetoacetic acids. Normally these acetone bodies are oxidized by the tissues to furnish heat and energy. There is a limit, however, to the capacity of the body for utilization of these end products of fat cata-

equal it, being about two thirds that of the individual in the general population at ages 40 and above

The result of this lengthening of life has been to render the diabetic liable to many more complications, both diabetic and non diabetic in nature He has become increasingly susceptible to arteriosclerosis and to disease conditions resulting therefrom as they affect particularly the heart brain, kidneys and peripheral vessels The presence of diabetes contributes to the early onset, frequency and severity of arteriosclerosis as seen in diabetics as compared with non diabetics By virtue of living longer the diabetic is allowed to develop other diseases such as cancer which affect all individuals in middle life and beyond The result of all of this has been a changing character in the practice of medicine among diabetic patients The physician treating diabetic patients needs above all to be a competent internist and use of the term "diabetic specialist should be discouraged When one deals with large groups of patients with diabetes one encounters all of the situations met with in practice in similar age groups of persons everywhere The internist in charge of the welfare of diabetics will need frequently the cooperation of the surgeon with both general and special interests the opthalmologist, the roentgenologist the dentist, the chiropodist and others with special interests, training and experience All must cooperate in an attempt to secure for the diabetic a longer happier and more useful life

Diabetic Coma

The term 'diabetic coma is used commonly to designate the more severe cases of diabetic acidosis even though the patient may not be totally unconscious It is difficult, therefore to set up hard and fast rules as to which acidotic patients shall be spoken of as having diabetic coma Some have proposed a classification based upon the degree of drowsiness but decision as regards this depends upon personal judgment Furthermore, experience has shown that not always is the state of the sensorium a reliable guide as to prognosis In practice it works out well to base the classification on the carbon dioxide content of the blood plasma classifying a case as one of diabetic coma if the value is 20 volumes per cent (9m M per liter) or lower This method of classification is arbitrary and may be at fault in a certain few cases but practically it has stood the test of time

Diabetic coma represents the end result of uncontrolled diabetes in the acute sense just as arteriosclerotic complications represent the end result over a long period of time In the pre insulin days more than 60 per cent (actually 63 8 per cent of 3 7 deaths 1898 to 1914) of all deaths in diabetics were in coma[a] This fact is apt to be lost sight of today by both physicians and patients because treatment seems so easy and at the moment complications may seem relatively remote At the present time thanks to insulin deaths from diabetic coma are relatively uncommon Of 651 deaths in diabetics from 1944 to 1949 only 1 9 per cent were in coma In the pre insulin days diabetic coma was the

TABLE XXI
DECLINE IN PERCENTAGE OF DEATHS DUE TO COMA
(106 3 fatal cases)

Period Years	*Total Deaths Number*	*Deaths Due to Coma Number*	*Per Cent*
1898 – 9 4	3 6	08	63 8
1914 – 19 2	836	4	41
19 2 – 1 6	4061	340	8.4
1937 – 1943	3151	98	3
1944 – 1949	99	43	1.9

Experience of Joslin and associates Statistics compiled with the cooperation of the Statistical Bureau of the Metropolitan Life Insurance Company

almost inevitable culmination of a diabetic life and it was the unusual diabetic child who lived longer than two years Now diabetic children are living on and on although it must be admitted that after 1 0 or 5 years of diabetes they are experiencing serious difficulties with degenerative vascular disease

Despite this lowered incidence of diabetic coma it remains always a potential menace and hazard Despite the fact that it is a preventable condition even today it occurs all too frequently Furthermore despite more than 25 years of experience with insulin inadequate doses often are administered and deaths result from poorly planned treatment

Pathogenesis — As has been discussed somewhat in detail in the section on Physiology in the normal person fats are broken down in the liver to form the so called acetone bodies beta hydroxybutyric and acetoacetic acids Normally these acetone bodies are oxidized by the tissues to furnish heat and energy There is a limit however to the capacity of the body for utilization of these end products of fat cata

bolism In the normal person carbohydrate is used preferentially but in the diabetic, when stores of carbohydrate are low and the capacity for utilization of such is impaired greater recourse must be had by the body to fats Consequently, acetone bodies are formed in larger amounts than can be used and therefore accumulate in the blood and body fluids and are excreted in the urine When this condition develops, a state of acidosis is said to be present which if unchecked, leads to diabetic coma and eventually to death

The body has certain natural defenses which enable it to withstand a certain amount of increase in the acetone bodies Part of the ketone acids can be excreted as free acid in highly acid urine and part may be neutralized by ammonia and excreted By virtue of the buffer action of the blood bicarbonate and the blood proteins including hemoglobin a considerable amount of the ketone acids can be taken up without significant change in the pH of the blood As long as the accumulation of ketone bodies can be handled by the means just cited, no serious effect is had upon the body However if these defenses are overwhelmed then the body resorts to neutralization of the ketone acids by fixed bases, chiefly sodium and excretion in the urine This process involves a loss of electrolytes, loss of fluid takes place and dehydration results Due to loss in the urine or to shifts within the body a lowered serum potassium may result[75] As emphasized by Guest[6] the rapid development of severe acidosis may be accompanied by a marked excretion of phosphates which, it is stated, is due chiefly to the break down of labile organic phospate in the blood and tissue cells The excretion of potassium accompanies that of phosphates Other electrolytes lost from the body during the development of severe acidosis include chlorides This takes place by means of vomiting by marked diuresis and possibly in part by the replacement of the chloride ion by the oxybutyric anion and the subsequent excretion of chlorides as ammonium chloride

The end results of the above processes are (1) depletion of fixed base chonide and phosphate of the body, (2) lowering of the plasma CO content (3) hemoconcentration and dehydration (4) shift in the pH of the blood toward the acid side (5) depletion of glycogen stores in liver and muscles

Etiology —Diabetic acidosis and coma arise because of (a) too much food (b) too little insulin (c) infections and (d) other complications as thyrotoxicosis which increase the rate of metabolic processes Over

eating may mean the deliberate breaking of diet of the patient who is under treatment for diabetes or the innocent overindulgence of the person with unrecognized diabetes Not infrequently the presence of diabetes is not discovered until the patient is brought to the doctor or to the hospital acutely ill in diabetic coma Too little insulin often means no insulin because it is a fact, fortunate or unfortunate that most diabetic patients carry along without the development of actual coma provided they take minimal even though inadequate doses of insulin Infections are a real menace a patient may be progressing serenely with diet and insulin well balanced when an acute infection particularly with fever suddenly throws the condition out of control Added to this is the fact that patients often reason that if they are ill and take little or no food they should not take their insulin and so omit it The fact is that despite lowered food intake the patient with an infection often requires as much as or even more insulin than he normally does Patients must be taught again and again never to omit insulin unless tests of the urine taken at regular intervals show the absence of sugar Thyrotoxicosis complicating diabetes creates a situation which demands the most careful attention on the part of the patient and the physician

Patients and physicians alike must be taught that diabetic coma is always preventable provided sufficient care is taken and that if treated early and energetically enough it is always curable

Symptoms—The onset of diabetic coma usually is gradual taking place over a matter of hours or days Since acidosis usually is preceded by a period of poor control of diabetes the patient often experiences prodromata consisting of thirst polyuria malaise and easy fatigability This is followed by anorexia nausea and often vomiting generalized adbominal pain and aches and pains particularly in the extremities If proper treatment is not instituted rapid deep labored breathing of the Kussmaul type begins Drowsiness appears and deepens progressively until finally total unconsciousness results

Signs—The patient in full blown diabetic coma presents a striking clinical picture He lies markedly drowsy or unconscious often moaning as with pain At intervals he may vomit quantities of dark liquid obviously changed blood perhaps with food remains The breathing is as described above except that in the last stages Kussmaul respiration may give way to the shallow feeble breathing of the moribund Examination shows marked signs of dehydration as evidenced by dryness and inelasticity of the skin marked dryness of the mucous membranes of the mouth and throat and softness of the eye balls The tongue is exceed

ingly dry and presents a dirty brownish coat The breath has the smell of acetone though some experience is necessary for detection of this odor The gums present a dry, purplish-red appearance, are swollen and the teeth may be loose The extremities are cold and mottled, the pulse may be weak and rapid and the blood pressure low, in fact so low that in extreme cases it may be most difficult to obtain a reading The veins are collapsed, and it may be difficult to secure sufficient blood for chemical determinations Along with these signs of circulatory collapse and shock one usually finds a low body temperature 97 F or below If fever is present one immediately suspects a complication The abdomen may be distended, and often signs of a dilated stomach are present, although there is generalized soreness no localized tenderness can be made out The tendon reflexes are diminished and the extremities are flaccid

Urine —Early in the development of diabetic acidosis the urine is increased in volume, but as dehydration increases the volume becomes less and the urine more concentrated The urine contains much sugar and large quantities of diacetic (acetoacetic) acid and acetone as shown by a positive ferric chloride (Gerhardt) reaction or a positive sodium nitroprusside (Rothera) test Usually the urine gives a positive test for albumin and examination of the sediment reveals "showers" of granular casts Only in those patients in which there is an associated renal block does one obtain a negative test for acetone bodies in the urine and in these cases the blood plasma yields a positive test

Blood —The blood sugar in well marked diabetic acidosis and coma is definitely elevated and usually although by no means invariably in direct proportion to the severity of the acidosis and gravity of the situation The initial blood sugar at the time the patient is presented for treatment averages about 500 mgm per 100 c c Values between 500 and 1 000 mgm per 100 c c are common and infrequently patients are seen with initial values of 1,000 mgm or above In the experience of the writer and his associates there were 24 such cases among 651 cases of diabetic coma, of these 19 recovered and 5 died The highest blood sugar value with recovery of the patient was 1,680 mgm per 100 c c [8]

The carbon dioxide content of the blood is markedly reduced often to the level of 10 to 15 volumes per cent (5 to 7 m M per liter) One may determine either the CO_2 content or the CO_2 combining power of the blood plasma although in general the former value gives information of more value Blood drawn for CO_2 content must be taken and kept under oil It goes without saying that in diabetic coma the blood

contains large amounts of acetone bodies The quantities present usually are proportional to the severity of acidosis Whereas in the normal person or the controlled diabetic values for total acetone bodies (acetone diacetic acid and beta oxybutyric acid) in the blood plasma are less than 5 mgm per 100 c c, values in diabetic coma range from 60 to approximately 00 mgm per 100 c c

It is common to find an elevation in the nonprotein nitrogen content of the blood and values from 40 to 60 mgm per 100 c c are seen frequently Occasionally particularly in advanced cases values over 100 mgm are found Additional changes in the blood include a lowering in the content of chloride sodium and potassium Accompanying the decrease in electrolyte content of the blood is a lowering of the freezing point of the serum An increase in the white blood count even in the absence of infection is common and values ranging from 15 000 to 50 000 per cu mm are seen frequently As far as patients with uncomplicated coma are concerned the highest count known to the writer was 9 000 per cu mm This leucytosis undoubtedly is due in part to the dehydration present as is most certainly the increase in red blood count and hemoglobin which is seen frequently prior to the beginning of treatment

Differential Diagnosis—When the patient is a known diabetic and is brought in an unconscious state the possibility of diabetic coma comes quickly to mind However when an unconscious patient unknown to the physician is brought to a hospital in which there is no more than the usual interest in diabetes the problem becomes more difficult In this situation the diagnosis of diabetic coma is made easily if the possibility is kept in mind and appropriate laboratory tests carried out promptly to confirm clinical impressions The differential diagnosis of diabetic coma includes the following severe hypoglycemia cerebral hemorrhage uremia meningitis and other overwhelming infections and chemical poisonings as from salicylates or barbiturates taken in over dosages The history physical examination and laboratory tests will serve to differentiate these various conditions

In diabetic patients taking insulin the differentiation most commonly necessary in the unconscious patient is between diabetic coma and hypoglycemia due to insulin The correct diagnosis is vitally important in a literal sense If hypoglycemia is mistaken for diabetic coma and additional doses of insulin given death may result On the other hand if diabetic coma is mistaken for hypoglycemia and glucose but not insulin is given a fatal result also may follow Experience holds examples of

ingly dry and presents a dirty brownish coat The breath has the smell of acetone though some experience is necessary for detection of this odor The gums present a dry, purplish-red appearance, are swollen and the teeth may be loose The extremities are cold and mottled, the pulse may be weak and rapid and the blood pressure low, in fact so low that in extreme cases it may be most difficult to obtain a reading The veins are collapsed, and it may be difficult to secure sufficient blood for chemical determinations Along with these signs of circulatory collapse and shock one usually finds a low body temperature, 97 F or below If fever is present one immediately suspects a complication The abdomen may be distended, and often signs of a dilated stomach are present, although there is generalized soreness no localized tenderness can be made out The tendon reflexes are diminished, and the extremities are flaccid

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Blood—The blood sugar in well marked diabetic acidosis and coma is definitely elevated and usually although by no means invariably, in direct proportion to the severity of the acidosis and gravity of the situation The initial blood sugar at the time the patient is presented for treatment averages about 500 mgm per 100 c c Values between 500 and 1 000 mgm per 100 c c are common and infrequently patients are seen with initial values of 1 000 mgm or above In the experience of the writer and his associates there were 24 such cases among 651 cases of diabetic coma, of these 19 recovered and 5 died The highest blood sugar value with recovery of the patient was 1,680 mgm per 100 c c [8]

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TABLE XVII

DIABETIC COMA vs HYPOGLYCEMIC COMA DIFFERENTIAL DIAGNOSIS IN THE UNCONSCIOUS PATIENT (from Marble[17])

Diabetic Coma	*Hypoglycemic Coma*
History	
Slow onset over a period of hours or days brought on by dietary indiscretions *inadequate insulin dosage* infections thyrotoxicosis or may appear as the first sign of a hitherto unrecognized diabetes Onset often with marked thirst nausea vomiting abdominal pain Then follow rapid deep breathing and drowsiness leading to unconsciousness	Rapid onset over a period of minutes (although with protamine zinc or NPH *insulin may come on more slowly*) Brought on by too much insulin too little or poorly absorbed food or physical exercise unusual for the patient Nausea and vomiting although uncommon may occur especially in reactions due to protamine zinc insulin
Physical Findings	
Body temperature subnormal unless infection present Skin dry mucous membranes and tissues show signs of dehydration eyeballs soft Patient extremely ill may be restless and moaning as with pain Respiration deep and labored (Kussmaul) except in preterminal stages Pulse weak and rapid blood pressure tends to be low	Body temperature usually normal Skin moist clothing often soaked with perspiration Normal hydration of tissues tension of eyeballs normal Convulsions may be present Respiration normal Blood pressure tends to rise in certain stages
Laboratory Findings	
Much sugar acetone and aceto acetic acid in blood and urine Plasma CO low	No sugar in urine (second specimen) low blood sugar normal plasma CO
Treatment	
Insulin fluid salt glucose and supportive measures produce gradual improvement	Glucose parenterally brings about prompt recovery Treatment may require repetition in reactions due to protamine zinc or NPH insulin

If it is learned that a patient at home is to be brought to the hospital and if on competent advice it seems certain that diabetic coma is present instructions may be given for a preliminary dose of 40 to 50 units of regular or crystalline insulin to be given prior to admission

Personnel at the hospital should be alerted so that when the patient is admitted treatment begins Upon admission the patient should be placed in a warm bed If relatives or friends are present an adequate history should be taken quickly A rapid yet complete physical examination should be carried out Urine should be obtained by catheter if necessary and tested immediately for sugar and diacetic acid Blood should be drawn for the necessary chemical tests and the values for the

each of these types of errors Fortunately a determination of the blood sugar will clear up the confusion quickly In situations in which the physician cannot secure laboratory aid within reasonable length of time it is permissible to inject intravenously 20 c c of 50 per cent glucose in buffered sterile solution However, if this and perhaps a subsequent injection 10 to 15 minutes later do not bring about a complete return of consciousness no further time should be lost and laboratory assistance obtained forthwith regardless of inconvenience

In the usual case the history and physical findings will give the trained observer an accurate idea of the diagnosis Whereas an insulin reaction particularly due to rapidly acting insulin comes on quickly over a period of minutes or hours diabetic coma progresses more gradually over a matter of hours or days A patient who awakens in the morning with a sugar free urine and feeling well, does not become unconscious due to diabetic coma during the forenoon It must be kept in mind that reactions due to protamine zinc and NPH insulin come on more gradually than those due to unmodified insulin Furthermore, reactions due to protamine zinc and NPH insulin at times may be accompanied by nausea and rarely by vomiting thus adding somewhat to the confusion of differential diagnosis In Table XVII are listed the chief points to be borne in mind in distinguishing between diabetic coma and an insulin reaction

At times the combination of nausea, vomiting and abdominal pain may bring up the question of acute appendicitis In a diabetic patient with acidosis differentiation usually can be made by virtue of the fact that the tenderness in diabetic coma is more apt to be generalized and not localized as in acute appendicitis Abdominal pain usually precedes nausea and vomiting in appendicitis whereas the reverse usually is true in acidosis In the absence of localized and definite abdominal tenderness it is wise to defer operation unless abdominal symptoms persist for a few or several hours after adequate treatment with insulin

Treatment —The patient with diabetic coma deserves treatment in a hospital just as much as does the patient with acute appendicitis Treatment must be carried out in a place in which adequate facilities exist not only for constant and careful nursing care but also for the giving of foods parenterally and the carrying out of laboratory studies including those of the blood and urine Diabetic coma is a true medical emergency in which treatment given within the first 3 to 6 hours is all important The physician must remain in constant attendance until the recovery of the patient seems assured

found hypoglycemia Consequently the size of doses must not be gauged solely by the number of units but by the effect secured An unwarranted fear exists as to producing hypoglycemia by the use of large doses No one would deny that care and common sense must be used always but the usual error is to give too little rather than too much insulin

The doses referred to above are those applicable to adult patients in full blown coma Smaller doses must be used in children in patients with recent onset of diabetes and those with mild degrees of acidosis

In the usual case it will be necessary to obtain a third determination of the blood sugar and CO content in 5 to 6 hours after admission By this time in the average patient both the clinical condition and the results of laboratory tests should show an unmistakable return toward normal If not then the indication is clear cut as to the need for even larger doses of insulin regardless of the amounts heretofore given When the clinical condition and the blood sugar value indicate that the major portion of the battle has been won then the administration of insulin may be governed by periodic tests of the urine for sugar

Tests may be obtained first at 1 or hourly and later at 3 hourly intervals and unmodified insulin given according to some such schedule as the following

If urine test is	Red or Orange	Yellow	Yellow green	Green or Blue
Give regular or crystalline insulin units	0	16	12	0

In the usual case such tests will need to be continued for perhaps a 1- hour period and then regulation with protamine zinc or NPH and unmodified insulin begun in the usual fashion

It need not be emphasized that during the period of acute acidosis the types of insulin used should be either regular or crystalline because of the immediate sharp effect desired Some have advocated the giving also of a dose of protamine zinc insulin early in treatment to serve as a sort of bacl log However this is not necessary for success and may confu e somewhat treatment with unmodified insulin in the first 1 to -4 hours

Fluid and Electrolytes —An adequate dose of insulin is all important

blood sugar and CO content should be reported to the physician within 30 to 45 minutes Later the physical examination should be repeated, particularly if hidden infection appears to be present

Insulin —If on admission, the history and physical findings seem to make the diagnosis of diabetic coma certain, and if the urine contains sugar and diacetic acid then a preliminary dose of regular or crystalline insulin should be given at once For the adult patient this should be at least 50 and usually 100 units Within 45 minutes the results of the blood tests should be available and additional insulin then should be given depending upon initial level of the blood sugar Experience has shown that some such schedule such as that which follows may be used to advantage

Initial blood sugar mg per 100 c c	Additional insulin to be given within first hour after admission *Units*
400-600	100
600 1000	200
1000 or above	300

In 2 to 3 hours after the initial dose of insulin a second determination of the blood sugar and CO content should be made These values will afford an indication as to whether the amount of insulin given so far has been adequate or inadequate and subsequent doses can be gauged accordingly If values for blood sugar are not falling an additional 50 to 200 units or more should be given The gravity of the case may require repetition of the first hour s total insulin as early as the second hour

In using insulin in diabetic coma these facts must be kept in mind

(a) To assure maximum success in treatment, truly adequate amounts must be given early i e within the first 3 hours after the patient is seen This procedure supplies large enough quantities of insulin to overwhelm opposing forces making available the glucose which is flooding the blood and body fluids and stopping at the source the formation of acetone bodies in abnormal amounts

(b) Insulin in times of acidosis is like paper money in times of inflation and cannot be taken at its face value Insulin in doses of 50 or 100 units may have relatively little effect upon a patient in acidosis and yet a week later following recovery would most surely bring about pro

found hypoglycemia Consequently the size of doses must not be gauged solely by the number of units but by the effect secured An unwarranted fear exists as to producing hypoglycemia by the use of large doses No one would deny that care and common sense must be used always but the usual error is to give too little rather than too much insulin

The doses referred to above are those applicable to adult patients in full blown coma Smaller doses must be used in children in patients with recent onset of diabetes and those with mild degrees of acidosis

In the usual case it will be necessary to obtain a third determination of the blood sugar and CO_2 content in 5 to 6 hours after admission By this time in the average patient both the clinical condition and the results of laboratory tests should show an unmistakable return toward normal If not then the indication is clear cut as to the need for even larger doses of insulin regardless of the amounts heretofore given When the clinical condition and the blood sugar value indicate that the major portion of the battle has been won then the administration of insulin may be governed by periodic tests of the urine for sugar

Tests may be obtained first at 1 or hourly and later at 3 hourly intervals and unmodified insulin given according to some such schedule as the following

If urine test is	Red or Orange	Yellow	Yellow green	Green or blue
Give regular or crystalline insulin units	0	16	12	0

In the usual case such tests will need to be continued for perhaps a 12 hour period and then regulation with protamine zinc or NPH and unmodified insulin begun in the usual fashion

It need not be emphasized that during the period of acute acidosis the types of insulin used should be either regular or crystalline because of the immediate sharp effect desired Some have advocated the giving also of a dose of protamine zinc insulin early in treatment to serve as a sort of back log However this is not necessary for success and may confuse somewhat treatment with unmodified insulin in the first 1 to 4 hours

Fluid and Electrolytes—An adequate dose of insulin is all important

in the successful treatment of diabetic coma and all other measures will fail unless enough insulin is given early However, there are secondary measures of great importance, first of which is the giving of fluids and electrolytes to restore what has been lost during the development of acidosis As has been discussed already various electrolytes are lost to the body but in the process of replacement success can be achieved by the giving of adequate amounts of physiological solution of sodium chloride As soon as possible after admission an intravenous injection of salt solution is started and allowed to continue until in the average case 2 000 or 3 000 c c have been administered, taking perhaps 3 to 5 hours for such In certain patients with more severe acidosis and in whom dehydration is extreme amounts up to 4 5 6 or more liters in 24 hours may be required In using salt solution one realizes that one is supplying only water sodium and chloride it has been suggested that more complex solutions containing other electrolytes, including potassium may be helpful (Butler[128]) However, temporarily salt solution alone is effective and soon brings sufficient improvement so that other deficiencies may be made up by food and fluid given by mouth

In the combating of circulatory collapse the giving of salt solution continuously has proved as effective as any other means Theoretically one might suppose that whole blood or plasma transfusions would be efficacious but experience has shown that these agents usually confer no additional benefit

Glucose and Food —There are some who advocate the giving of solutions of 5 or 10 per cent glucose from the outset of treatment However the writer and his associates [8] firmly believe that in the average case of diabetic coma the giving of glucose has no place in the first 3 to 6 hours of treatment In some patients this may be harmful and in almost all cases in which such therapy is used it serves to divert the attention of the clinician away from the all important matter of giving enough insulin

No one would argue that the hourly administration of 5 or 10 grams of glucose intravenously or that the giving of glucose after the first 6 hours when the acute condition has been overcome would be injurious The plea is against an all too common practice of giving much larger amounts of glucose from the very beginning of treatment The reasons for such are as follows

(1) The blood and body fluids generally are already flooded with glucose in high concentration To a greater or less degree this glucose is

metabolically inert due to the lack of insulin There is nothing to indicate that this glucose is not potentially as valuable to the body as any which can be injected The urgent need is to make it available for utilization by the body by admitting it to the metabolic system through phosphorylation There is only one agent which can do this namely insulin in sufficient amounts to overcome opposing forces[16, 17] Until this is done the addition of glucose to the body only adds insult to injury

(2) If one is giving glucose by vein it is difficult to interpret the results of periodic determinations of the urine and blood sugar which are a useful and almost indispensible guide to treatment

(3) In diabetic coma one is dealing with an individual in whom the pancreas already is severely overworked It seems illogical to impose an additional burden

(4) In certain cases it has appeared that the giving of glucose has favored renal block

(5) The administration of glucose may so promote diuresis that even larger amounts of potassium than usual are lost from the body The hazard of a low blood potassium will be discussed in a subsequent section

The argument that the giving of glucose in treatment may help in the disposition of glycogen does not appear valid in a practical sense The important thing at this stage is that glucose be rendered metabolically active by means of adequate amounts of insulin Finally the argument that glucose should be given to avoid hypoglycemia due to overdosage with insulin has not been borne out by experience If judgment and common sense are used in the selection of the large doses of insulin rarely will dangerous hypoglycemia occur

It is important that as soon as the patient is able to take fluids by mouth these be started Such is often possible within 3 to 6 hours after initiation of treatment One starts at first with water and then if this is tolerated broth tea with sugar then gruel orange juice and ginger ale may be given in small amounts at first 100 to 150 c c an hour Such fluids provide to a greater or less degree valuable electrolytes including potassium Amounts of fluid may be increased gradually as tolerated by the patient and usually in 12 to 18 hours the patient is able to take soft-solid food Gradually over a period of 2 or 3 days return to a normal diet usually is possible

Potassium — Since the report of Holler[5] in 1946 regarding the association of a low blood potassium with muscular including respiratory paralysis much has been said and written regarding the use of

potassium in the treatment of diabetic coma. Studies have shown that due chiefly to dehydration in patients with untreated diabetic coma the concentration of potassium in the blood serum is often somewhat greater than the normal of 4.1 to 5.1 mEq. per liter. Then as treatment with insulin and fluids is carried out, the serum potassium falls because of dilution, excretion in the urine and passage into body cells. The lowest serum concentrations occur usually in 6 or 8 up to 12 or 18 hours after the beginning of treatment and may be below 3.0 mEq. per liter. In the presence of a low serum potassium there may occur changes in the electrocardiogram consisting of lengthening of the QT interval, depression of the ST segments and inversion of the T waves. Hence, changes in serial tracings may be used as a rough though not infallible guide in treatment, if facilities are not available for the determination of serum potassium. The writer and his associates believe that, if patients are not given glucose during the first few hours of treatment, and if favored by early gastric lavage, patients are started as soon as possible (often 5 or 6 hours after initiation of treatment) on oral feedings of natural foods (broth, gruel, orange juice, etc.) the likelihood of symptomatic hypokalemia is extremely small. However, if muscular weakness or paralysis and cardiovascular manifestations occur along with a low serum potassium, then one may give potassium chloride orally or intravenously. In our own cases we have not given over 3 grams orally over a period of 3 hours. Nadler and associates[123] in giving potassium chloride intravenously used initially up to 6.0 grams total in a solution containing 155 mEq. per liter. Potassium should not be given unless the serum level is below normal. Its use also is definitely contraindicated in the presence of poorly functioning kidneys or oliguria because of the real danger of potassium intoxication.

Alkalies.—For years there has been a controversy regarding the use of alkalies in the treatment of diabetic coma. At the George F. Baker Clinic no alkalies have been used during the insulin era. From May 1923 to January 1946 651 instances of diabetic coma (in 495 patients) were treated with 61 deaths, a case mortality of 9.4 per cent. From January 1940 to January 1946 there were 188 cases of diabetic coma with only 6 deaths, a mortality of 3.2 per cent. There were no death among 9 consecutive cases of coma from April 1945 to April 1948. These hopeful figures have lent weight to the argument that alkalies are not necessary in the treatment of diabetic coma. It is believed that in some cases they may be actually harmful because of the possibility of producing

alkalosis In any case their administration acts only to neutralize acetone bodies already formed and does not correct the abnormal process at its source Those who use alkalies maintain that acidosis is overcome more quickly and that patients become comfortable sooner However if truly adequate doses of insulin and salt solution are given early in treatment improvement takes place in the average case promptly Alkalies suitable for intravenous administration include sterile buffered 5 per cent sodium bicarbonate solution, sodium lactate solution or combinations of these

Gastric Lavage—In most cases it is profitable to wash out the stomach shortly after admission Usually one is rewarded by the finding of large amounts of dark brown fluid often containing food remains Such practice lessens the tendency to nausea and vomiting and relieves abdominal distention If the stomach is lavaged on admission one is able to start fluids and foods by mouth early

Enema—A cleansing enema within the first few or several hours of treatment usually is indicated and helps relieve abdominal distention

Accessory Medication—In circulatory collapse stimulants such as epinephrine 0 3 to 1 c c of a 1 1 000 solution subcutaneously or ephedrine sulphate 4 mgm subcutaneously may be given as well as caffeine sodium benzoate in appropriate dosage Rarely does one see dramatic or lasting benefit from such

Prognosis—Diabetic coma is a preventable condition Once coma has developed the condition is curable provided adequate treatment is begun early enough The prognosis becomes increasingly grave the longer the duration of coma and the severer the acidosis Patients with highest blood sugar values and with lowest CO_2 values likewise have a poorer prognosis Circulatory collapse is always a feature to be feared However, patients in circulatory collapse with extremely low blood pressure readings patients with blood sugar values of 1 000 mgm per cent or above patient with values for CO_2 content below 3 m M per liter and patients who have been unconscious for several hours all have recovered Hence no single finding can be regarded as absolutely decisive in prognosis It is the total situation which is of importance and no case should be regarded as hopeless

Earlier diagnosis and the more liberal use of insulin the first 3 hours of treatment are believed by the writer and his associates at the George F Baker Clinic to be responsible for the lessened mortality in cases of coma treated at the New England Deaconess Hospital Among a total

of 677 cases treated from 1923 to 1947 the mortality was 12 per cent in those seen from 1923 to 1940 and only 1 5 per cent from 1940 to 1947 The average number of units given the first 3 hours after admission in certain periods was as follows

	1923-1927	1932 1933	194? 1947
Insulin in first 3 hours, units	83	136	06
Mortality per cent	18	.2	1 5

Total unconsciousness by no means precluded recovery This and the improvement in results in recent years are shown in Table XVIII

TABLE XVIII

MENTAL STATE AND MORTALITY IN COMA

	1923 1939		1940 1947	
Mental Condition	*Cases No*	*Mortality Per Cent*	*Cases No*	*Mortality Per Cent*
Conscious	187	3	39	[illegible]
Semi conscious	18	8 8	130	0 7
Unconscious	83	35.0	42	9 4
Totals and Averages	45	11	211	2 7

Youth confers a definite advantage Young people withstand the insult of diabetic coma better than do older individuals with varying degrees of cardiovascular renal disease It requires neglect and poor treatment to allow death from diabetic coma in a child

One serious complication directly related to acidosis is of great importance If renal block with oliguria or anuria and rising blood non protein nitrogen occurs the outlook is poor, and all possible steps should be taken to reestablish kidney function In a certain few of these cases anuria has seemed to be related to a low blood chloride and in these Root [9] has reported that recovery has taken place following the use of 60 to 130 c c of 10 per cent solution of sodium chloride intravenously

It is evident if a complication exists which is in itself fatal, death will occur which must be credited to diabetic coma However, with the availability of the sulfonamides penicillin streptomycin and other newer therapeutic agents the physician now has the means to combat successfully many complications which formerly led to a fatal outcome

Hypoglycemia Due to Insulin

Perhaps the most common complication in the present day in the treatment of diabetes is an insulin reaction Such attacks are important because although they usually are not serious they are apt to cause the patient and his family great concern and result in inconvenience embarrassment and loss of self confidence

An insulin reaction is due to an overdose of injected insulin the taking of too little food or unusual exercise Reactions due to unmodified (regular or crystalline) insulin usually take place within 3 or 4 hours after administration whereas those from protamine zinc insulin occur within 1 to 4 hours after the dose has been given Reactions due to globin insulin most commonly take place from 7 or 8 hours following injection This means that hypoglycemic attacks due to globin insulin which has been given in the morning before breakfast are most apt to recur in the mid afternoon This is true also of those caused by NPH insulin

Symptoms—Reactions due to unmodified insulin come on rapidly over a matter of minutes Symptoms include sweating nervousness tremor rapid heart action double vision numbness about the lips and mouth hunger faintness and dizziness There may be emotional disturbances such as irritability laughing or crying without due cause In severe reactions unsteadiness of gait and muscle incoordination may occur Drowsiness leading to unconsciousness with or without convulsions may develop uncommonly Reactions due to protamine zinc insulin come on more slowly over a matter of hours and in individuals taking insulin in the morning before breakfast are apt to occur during the night or in the early morning hours Patients may fail to awaken in the morning at the usual hour or if they do awaken have certain of the symptoms described above and in addition may have nausea and at times vomiting These latter symptoms may make differentiation between hypoglycemia and diabetic coma more difficult

Signs—Physical examination in an individual with an insulin reaction reveals findings suggested by the symptoms outlined above As is brought out in Table XVII the body temperature the blood pressure and the general physical examination usually are not remarkable In more severe reactions extreme restlessness lack of cooperation and pugnaciousness of the patients may present a problem in treatment In the uncommon patient in whom total unconsciousness occurs there

may be found rarely transient hemiplegia, positive Babinski reactions and loss of sphincter control

Laboratory Findings—In an insulin reaction the blood sugar is low and almost invariably below 70 mgm per 100 c c Some have described symptoms of hypoglycemia with values well above this level, but one must look askance at such reports, although it is conceivable that certain symptoms characteristic of hypoglycemia might accompany a precipitous fall in blood sugar from a high to a much lower level In the range of blood sugar below 70 mgm per 100 c c there is no consistent correlation between the blood sugar value and the severity of the symptoms Some patients may experience symtoms at levels of blood sugar at which others are apparently not affected, and there may be a variation in a given individual from one time to another In general symptoms are less apt to occur, if persons are quiet and relaxed It is instructive that children with von Gierke's disease are relatively asymptomatic despite the characteristic chronic hypoglycemia of severe grade

The urine is free from sugar in patients having an insulin reaction One refers here to the urine as excreted by the kidney and not necessarily to that obtained from the bladder Thus if the patient has not voided for some hours the first specimen tests may contain sugar due to prior excretion and storage in the bladder whereas a second specimen obtained 20 to 30 minutes later may give a negative test This is a point which must be made clear to the patient

Treatment—The treatment of an insulin reaction consists in the giving of readily available carbohydrate Patients able to swallow may be given 10 grams of carbohydrate in the form of sugar, candy, orange juice ginger ale or other suitable food In the usual case relief of symptoms is prompt In the confused uncooperative patient more viscous material as corn syrup, may be administered At time the subcutaneous injection of 0 5 cc of adrenalin or surgical pituitrin is effective

In the unconscious patient resort must be had to the injection of glucose intravenously Vials containing 0 cc of 50 per cent glucose in a sterile buffered solution are commercially available and should be in the bag of every practitioner Usually the giving of one of these will bring about complete recovery and often the effect is most dramatic At times particularly in dealing with reactions due to protamine zinc or NPH insulin oral or intravenous feedings must be repeated once or twice In cases in which glucose cannot be given intravenously the subcutaneous route using a 2½ or 5 per cent solution may be employed

The absorption of glucose from the colon is so variable and so open to question that it is not to be recommended unless other routes are not possible

Treatment of Prolonged Hypoglycemia —Rarely one sees patients in whom unconsciousness due to hypoglycemia has persisted several hours and in whom the usual measures have not been effective Not infrequently the condition is the result of erroneous diagnosis in an unconscious patient and the administration of insulin to a person already in hypoglycemia By the administration of glucose intravenously it is possible to raise the blood sugar to a normal level and to maintain it at that or higher levels Despite this unconsciousness persists presumably due to irreversible damage to the central nervous system Nerve tissue is peculiar in that it utilizes only carbohydrate and does not store it as glycogen Consequently it is dependent upon the sugar in the blood and when the level of this is low for a prolonged period anoxia with resulting brain damage results Patients may die within a few days or live for weeks or months Although vegetative bodily functions may be restored the activity of the higher brain centers is not reestablished Fortunately such instances are rare and since the condition is preventable need not occur at all

In the treatment of severe attacks just described one gives an injection of 5 or 10 per cent glucose constantly for the first hours or perhaps days of treatment in order to maintain the blood sugar level at or slightly above a normal level The intravenous injection may be given slowly so that excessive amounts of fluid are not administered Insulin is given in dosage adequate to control the diabetic condition yet not in amounts great enough to provoke hypoglycemia again If circulatory collapse is present as is often the case adrenalin in 1 1 000 solution may be added to the infusion in the proportion of 4 c c to 1 000 c c of glucose solution Oxygen administration may be used if cyanosis is present Barbiturates may be valuable aids in preventing convulsions Suction may be necessary to aspirate fluid which is in the bronchi resulting from pulmonary edema If lumbar puncture indicates the presence of cerebral edema hypertonic solutions of glucose sodium chloride or sucrose may be tried intravenously

Degenerative Vascular Disease

Much has already been said regarding the fact that with the prolongation of life made possible with insulin degenerative vascular

disease, chiefly arteriosclerotic, has traded places with diabetic coma as a cause of death and at the present time accounts for fully two thirds of all deaths in diabetics Arteriosclerosis affects the body generally and assumes great importance in its involvement of the heart brain, kidneys and extremeties

It has long been recognized that arteriosclerosis occurs at an earlier age and in more severe form in diabetics than in non diabetics In patients in middle and later life however, it is always difficult to differentiate effects incident to advancing age and other influences from those specifically related to diabetes Consequently, now that insulin has enabled persons with onset of diabetes under the age of 15 years to live 15, 20 and 25 or more years with the disease an unparalleled opportunity is afforded of studying arteriosclerosis in an age group in which it is uncommon in non diabetic individuals, at least to the degree that is recognizable clinically When one sees calcified arteries by x ray in a diabetic 60 years old, one never knows how much contribution diabetes has made to the pathological process, but if such finding is present in a diabetic 30 years of age it is of outstanding significance It is to patients with onset of diabetes in childhood that one must turn in order to observe the disease and its consequences in purest form

In a study of 200 patients with onset of diabetes at the age of 15 years or under and who had survived 20 years of diabetes, White[4] reported that vascular disease was demonstrated in 184 or 92 per cent In this group it was noted that the incidence of such complications did not reach an impressive figure until after survival of 15 years of diabetes The actual figures are given below with the findings listed by type of abnormality and per cent of cases involved

	Per Cent
Cerebral vascular accidents	2.5
Coronary insufficiency	8.0
Albuminuria	30.0
Hypertension	40.0
Nephritis	50.0
Calcified arteries (x ray)	75.0
Retinal hemorrhages	80.0
Retinal arteriosclerosis	85.0

It has been pointed out previously that vascular complications of diabetes come on only slowly after 10 15 or 20 years of the disease

Consequently short time studies of the effect of this or that therapeutic regime in the incidence of such complications are apt to be worthless

It is likely that the statistics just given are the worst possible because the individuals under consideration were the first to be treated in the insulin era and during the first half of this time many of them had diets which today would be considered suboptimal and until 1937 had the advantage of only unmodified insulin The experience of the future should be better because of the more continuous control of diabetes made possible with insulins of prolonged action It is the opinion of the writer and associates that the high incidence of vascular complications in diabetes is due to the metabolic disturbance of poorly controlled diabetes It is believed that if insulin could be supplied to the diabetic in truly adequate amounts mimicking Nature in its supply to the body these complications would not occur Just what it is about the disturbed metabolism of diabetes that is responsible for vascular disease is not clear Suggestions have included hypercholesterinemia chronic subclinical acidosis and other less well defined influences The high incidence of vascular complications in young diabetics is no doubt due to the fact that the disease in this age group is apt to be severe and the metabolic processes unusually labile Moreover with juvenile and adolescent patients it is more difficult to secure regularity as regards diet physical activity and other matters of importance in maintaining careful control of the diabetic condition

Encouraging is the fact that in those few patients in whom for over 20 years the diabetic condition has been controlled meticulously vascular complications are strikingly reduced or absent Joslin (paper to be published) recently analyzed the histories of twenty four patients who after twenty five or more years of diabetes had been awarded a medal because of freedom from degenerative vascular disease in the eyes heart kidneys and extremities as judged by careful examination by internists ophthalmologists and roentgenologists He found that this was by and large a group of persons who had been able to achieve careful and continuous control of their diabetic condition There is ample basis for holding up careful control of diabetes as the standard by which patients should live with relative freedom from complications as the reward

Because of their importance the various clinical syndromes caused by vascular disease deserve separate discussion under four headings as it affects principally the extremities heart kidneys and brain

disease, chiefly arteriosclerotic, has traded places with diabetic coma as a cause of death and at the present time accounts for fully two thirds of all deaths in diabetics Arteriosclerosis affects the body generally and assumes great importance in its involvement of the heart, brain, kidneys and extremeties

It has long been recognized that arteriosclerosis occurs at an earlier age and in more severe form in diabetics than in non diabetics In patients in middle and later life, however, it is always difficult to differentiate effects incident to advancing age and other influences from those specifically related to diabetes Consequently now that insulin has enabled persons with onset of diabetes under the age of 15 years to live 15, 20 and 25 or more years with the disease an unparalleled opportunity is afforded of studying arteriosclerosis in an age group in which it is uncommon in non diabetic individuals at least to the degree that is recognizable clinically When one sees calcified arteries by x ray in a diabetic 60 years old one never knows how much contribution diabetes has made to the pathological process, but if such finding is present in a diabetic 30 years of age it is of outstanding significance It is to patients with onset of diabetes in childhood that one must turn in order to observe the disease and its consequences in purest form

In a study of 200 patients with onset of diabetes at the age of 15 years or under, and who had survived 20 years of diabetes, White[1] reported that vascular disease was demonstrated in 184 or 92 per cent In this group it was noted that the incidence of such complications did not reach an impressive figure until after survival of 15 years of diabetes The actual figures are given below with the findings listed by type of abnormality and per cent of cases involved

	Per Cent
Cerebral vascular accidents	2 5
Coronary insufficiency	8 0
Albuminuria	30 0
Hypertension	40 0
Nephritis	50 0
Calcified arteries (x-ray)	75 0
Retinal hemorrhages	80 0
Retinal arteriosclerosis	85 0

It has been pointed out previously that vascular complications of diabetes come on only slowly after 10 15 or 20 years of the disease

9 After 50 years of age hearing and sight are often impaired the sense of feeling is diminished Remember this and be cautious about the feet

Treatment of Corns and Calluses

1 Wear shoes which fit and cause no pressure
2 Soak the foot in warm not hot soapy water Rub the dead skin from the callus or corn with gauze or by careful filing Do not tear it off Do not cut corns or calluses Do not try to remove corns or calluses with patent "corn cures"
3 Prevent calluses under the ball of the foot
   a by exercises such as curling and stretching the toes 0 times a day
   b by finishing each step on the toes and not on the ball of the foot

Aids in Treatment of Imperfect Circulation

1 Exercises Bend the foot down and up as far as it will go 6 times Describe a circle to the left with the foot 6 times and then to the right Repeat morning noon and night
2 Massage the feet with lanolin or cocoa butter
3 Do not wear circular garters or sit with the knees crossed
4 If you have had gangrene or been threatened with it keep off your feet 5 or more minutes each hour of the day and if you have had an amputation 15 minutes or more

Treatment of Abrasions of the Skin

1 Proper first aid treatment is of the utmost importance even in apparently minor injuries Consult your physician immediately
2 Avoid strong irritating antiseptics such as lysol and tincture of iodine
3 At once after an injury wash the wound well with soap and water then apply sterile gauze saturated with medicated alcohol or hexylresorcinol Keep wet for not more than 30 minutes by adding more of the antiseptic solution Sterile gauze in sealed packets may be purchased at drug stores
4 Elevate and as much as possible until recovery avoid using the foot
5 Consult your doctor for pain redness swelling or any inflammation

Symptoms—In the absence of open lesions on the feet and legs impaired circulation in the lower extremities may become manifest to the patient through pain aching or cramps in the calves or feet which come on with walking and are relieved by rest This intermittent claudication is often incorrectly diagnosed and not infrequently the patient is given treatment for fallen arches or other orthopedic conditions With progression of the process discomfort may come on with less and less aggravation and in extreme cases may be present constantly even at bed rest If with complete rest in bed for a period of 3 weeks the patient does not become comfortable the circulatory impairment is marked and the prognosis poor

Diagnosis—An accurate evaluation of the circulatory status in the extremities may be made without resort to special apparatus In addi

Arteriosclerosis of Peripheral Vessels Including Gangrene with and without Infection

Among what might be called specific surgical complications of diabetes infection and gangrene of the feet stand out most prominently In any hospital in which sizable groups of diabetic patients are treated it is common to find a high proportion of patients suffering from this type of disorder The premature arteriosclerosis encountered in diabetes results in impaired circulation to the lower extremities in a high proportion of middle-aged and elderly diabetics Because of this the feet are more vulnerable than those of non diabetics of comparable ages Breaks in the skin and infections are not overcome with normal speed and an apparently insignificant lesion may refuse to heal and eventually surgery of drastic nature may be required For this reason from the outset of treatment diabetics and their families must be taught in simple language rules for care of the feet These are given in detail in Table XIX

TABLE XIX

INSTRUCTIONS TO PATIENTS REGARDING THE CARE OF THE FEET (from Joslin and Associates[8])

Hygiene of the Feet

1 Wash the feet daily with soap and water Dry thoroughly especially between the toes using pressure rather than vigorous rubbing
When thoroughly dry rub with lanolin to keep the skin soft and free from scales but never enough to produce tenderness If the feet become too soft rub once a day with alcohol

3 If the nails are brittle and dry soften them by soaking the feet in warm water one half hour each night apply lanolin under and about the nails and bandage loosely Clean the nails with an orange wood stick Cut the nails only in a good light and after a bath when the feet are clean Cut the nails straight across to avoid injury to the toes If you go to a chiropodist tell him you have diabetes

4 All patients with overlapping toes or toes that are too close together should separate them by lamb's wool Patients with large joints or cramped up toes should wear shoes made of soft leather and without box toes

5 All patients over 60 years old should have daily rest periods during which they remove their shoes Regularly once a week ask someone to examine your feet

6 Do not wear bedroom slippers when you should wear shoes because slippers do not give proper support Do not step on the floor with bare feet

7 Wear shoes of soft leather which fit and are not tight (neither too narrow nor too short) Wear new shoes one half hour only on the first day increasing the time one hour daily

8 Use bed socks instead of hot water bottles hot irons hot bricks or electric heaters

9 After 50 years of age hearing and sight are often impaired the sense of feeling is diminished Remember this and be cautious about the feet

Treatment of Corns and Calluses

1 Wear shoes which fit and cause no pressure
2 Soak the foot in warm not hot soapy water Rub the dead skin from the callus or corn with gauze or by careful filing Do not tear it off Do not cut corns or calluses Do not try to remove corns or calluses with patent corn cures
3 Prevent calluses under the ball of the foot
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2 Massage the feet with lanolin or cocoa butter
3 Do not wear circular garters or sit with the knees crossed
4 If you have had gangrene or been threatened with it keep off your feet 5 or more minutes each hour of the day and if you have had an amputation 15 minutes or more

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4 Elevate and as much as possible until recovery avoid using the foot
5 Consult your doctor for pain redness swelling or any inflammation

Symptoms—In the absence of open lesions on the feet and legs impaired circulation in the lower extremities may become manifest to the patient through pain aching or cramps in the calves or feet which come on with walking and are relieved by rest This intermittent claudication is often incorrectly diagnosed and not infrequently the patient is given treatment for fallen arches or other orthopedic conditions With progression of the process discomfort may come on with less and less aggravation and in extreme cases may be present constantly even at bed rest If with complete rest in bed for a period of 3 weeks the patient does not become comfortable the circulatory impairment is marked and the prognosis poor

Diagnosis—An accurate evaluation of the circulatory status in the extremities may be made without resort to special apparatus In addi

tion to signs of poor nutrition such as thin inelastic skin the important features of the physical examination are as follows

(1) Palpation of peripheral arteries Attempts should be made to feel pulsations in the dorsalis pedis and posterior tibial arteries, if these cannot be felt then the popliteal and finally, femoral arteries should be palpated The dorsalis pedis arteries are remarkably constant from person to person As has been mentioned in the section on "Pathology", because of the usual slow progression of the sclerotic process one may at times find patients with adequate circulation in the absence of palpable main vessels because of the presence of collateral circulation

(2) Temperature A foot or leg with impaired circulation will feel cooler to the touch than will a normal extremity It is often possible to gain an idea as to the level of marked involvement by passing the hand up and down the leg and noting the point of temperature change

(3) Color changes When a patient with impaired circulation sits with the feet hanging down the color of the feet becomes abnormally red or purplish red and the veins become distended Often the patient will complain of pain after sustained dependency The patient should then be instructed to lie down, if the feet are elevated above the level of the body they quickly blanch and may become cadaveric in appearance with the veins appearing as tiny grooves If in this position the patient is asked to exercise the feet and toes, pain may be complained of quickly

In addition to these simple measures more elaborate means of evaluating the state of the circulation may be used Determination of the temperature of the skin under controlled conditions and the effect on such of measures designed to relieve vasospasm may be of help in deciding whether or not the circulation would be significantly improved through lumbar ganglionectomy At times readings obtained by an oscillometer may be helpful but in general the simple measures outlined above suffice for diagnosis and guidance in treatment

Treatment —Of prime importance in the treatment of the patient with circulatory deficiency is limitation of activity In less severe cases this may mean simply reducing the amount of active exercise to within the limitations imposed by pain In other patients it may mean complete bed rest for variable periods It must be kept in mind that the development of collateral circulation is favored by active exercise so that if a patient must remain at bed rest to keep comfortable a program of activity such as that provided by *Buerger exercises* should be carried

out With the patient lying in bed the legs are elevated on an inclined plane from 30 to 60 above the horizontal and allowed to remain there for ½ to 3 minutes the time prescribed according to the period found necessary to produce blanching Then the patient sits on the edge of the bed and allows the feet to hang down The length of time in this position is regulated according to the period required for the development of hyperemia and is usually from 2 to 5 minutes Ordinarily one sets a period of dependency one minute longer than necessary to establish a definite red color The legs then are placed in the horizontal position for 2 to 5 minutes The average schedule would include keeping the feet minutes in the elevated position 3 minutes in the dependent position and 5 minutes in the horizontal position Each cycle therefore would require 10 minutes with 6 cycles in an hour Most patients can to advantage perform such exercise 3 or 4 hours a day A suitable Buerger apparatus consists of two boards each ¾ inches thick 30 inches long and 11 inches wide hinged on one end In the middle of one board is a hinged tongue placed so as to fit over the cleats on the other board The apparatus can be opened at an angle of 30 45 or 60 degrees as desired An ordinary straight chair turned upside down and covered with a pillow may be used until a Buerger board is available

When an apparatus was introduced some years ago to carry out *passive vascular exercises* it was used extensively in diabetic patients Experience was not favorable Later on an apparatus for producing *intermittent venous occlusion*[1] was subjected to trial and at the present time some use is still made of this in selected patients The results are never dramatic and are usually difficult to evaluate but it is possible that in a certain few patients this type of treatment may be helpful The apparatus consists essentially of blood pressure cuffs connected with a machine which according to an automatic rhythmic cycle arranged by the operator provides alternate inflation and deflation of the cuffs one of which is placed about each thigh

Recently in addition to *lumbar ganglionectomy* which certainly has a place in the treatment of some patients other measures have been proposed with the thought of overcoming vasospasm These include

(1) The administration once daily over a period of two or three weeks of *diethyl ether intravenously* in the proportion of 5 c c of ether to 1 000 c c of normal salt solution or 5 per cent glucose This treatment devised and advocated by Katz[2] is stated to improve the circulation in

many patients to the extent that pain is relieved and surgery is not necessary. At the present writing the results of clinicians other than Katz have been disappointing.

(2) Treatment with histidine and ascorbic acid as advocated by Wirtschafter and Widmann[8]. This has not proved successful in the hands of others.

(3) Various drugs have been suggested for use either orally or parenterally to improve circulation. Among these is vitamin E (tocopherol), tetraethyl ammonium (etamon) and priscoline. The results obtained by use of these agents in older diabetic patients have been disappointing. Vitamin E would appear to have no good basis of its use. The other two agents do lessen vasospasm but have the disadvantage that their action is general and systemic so that unpleasant side effects may be obtained in the attempt to give enough of the drugs to secure a satisfactory local response in an extremity. Furthermore, it is difficult to obtain a consistent, continuous effect.

All too often by the time that the patient reaches the doctor or the hospital gangrene or infection or both are present in the extremities. Involvement of the toes is most common, although other parts of the feet and legs are frequently affected. A common story is that following minor trauma gangrene accompanied by infection occurred. Often the patient has continued at work despite indications of trouble and has relied upon ointments and other local therapy for relief. Experience has shown that in this situation the best single thing that the patient can do is to remain absolutely off his feet. Over and over again one finds that a lesion will improve markedly in the hospital with no more impressive treatment than complete bed rest. Patients at home often reason fallaciously that no great harm can come from getting up to go to meals, to the bathroom and from sitting in a chair for part of the day. In keeping patients at bed rest, care must be taken to keep the feet slightly lower than the level of the heart in order to prevent prolonged ischemia.

Rarely is local medication of prime importance. If an antiseptic is used, it should be something mild such as hexylresorcinol, and even this should be diluted 1:4. In acute stages ointments are rarely indicated, although in certain situations special preparations such as furacin ointment, cod liver oil ointment or chlorophyll ointment may be helpful. The last named ointment probably owes to its water-soluble base most of any effectiveness it may have.

In the presence of infection treatment consists of (1) complete bed rest ( ) such preliminary surgical steps as are necessary to secure adequate drainage (often these may be carried out without anesthesia with the patient in bed) (3) the use of the sulfonamides and antibiotics At the present time in the average case the preliminary medication of choice is penicillin given in intramuscular dosage of 300 000 to 800 000 in 4 hours Later this may be replaced or combined with streptomycin aureomycin terramycin or other agents as indicated by culture and sensitivity tests or by the clinical course The introduction of the antibiotics has changed greatly the outlook of the surgical diabetic lives have been saved and less drastic surgery made possible

After a few or several days on this regime it is usually possible to evaluate the situation much more intelligently By this time any edema will have subsided in whole or in part any lymphangitis will have decreased infection will have localized and the patient should have become more comfortable Now one can take account of stock and decide as to what surgical measures if any will be needed If gangrene is present or if osteomyelitis is evident from physical examination and x ray the issue is clear and some type of surgery must be carried out Amputation may be effected at the following levels (a) through or at the base of one or more toes (b) through the transmetatarsal bones (c) through the lower leg (d) through the lower thigh at the supracondylar level In deciding as to the level of amputation one must keep in mind not only the degree and level of impairment of circulation but also the age sex economic status occupation and probable life expectancy of the individual concerned

It is impossible to carry out successfully an amputation of a toe or toes unless the circulation in the foot is adequate Surgery of this type done in a foot with inadequate circulation will result only in a gangrenous wound which will not heal Up until recent years it was common practice based on years of experience to advise amputation through the lower thigh when toe amputation was not possible because of markedly impaired circulation However in the last several years a type of amputation through the transmetatarsal bones has been used more and more by McKittrick and associates[83] (see Fig 6) In the group of 12 people subjected to such surgery from 1944 to September 1947 are included many persons who formerly would have had lower thigh amputations" Patients with a transmetatarsal amputation have instead a lower leg and foot which are surprisingly serviceable requiring no more complicated apparatus than soft material in the end of

the shoe and perhaps a steel shank in the shoe to give more support It is obvious that operation at this level will not be successful in patients whose circulation is severely impaired, and for these the lower thigh amputation must still be carried out Among the 1-2 patients noted above failure to heal occurred in 22, and in 19 of these operations at a higher level was subsequently necessary These failures represented honest attempts after due consultation with the patient and his family

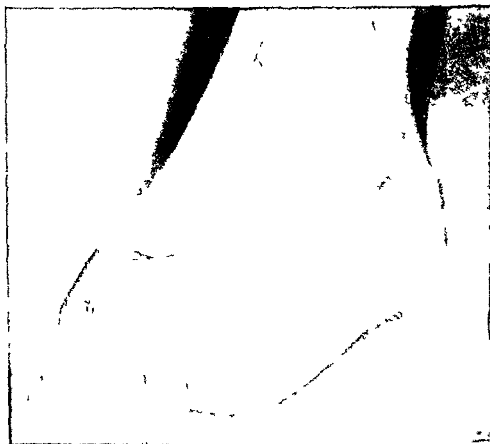


Fig 6 Stump of transmetatarsal amputation through left foot nine months after *operation for gangrene of the third toe (from McKittrick[93]) The patient* J McD was a man aged 78 years with diabetes of 3 years duration Although no pulsation was felt in the dorsalis pedis artery an excellent anatomical and functional result was obtained

to carry out less drastic surgery in situations which were admittedly unfavorable As time goes on and as experience accumulates, it should be possible to predict with more certainty those patients in whom the metatarsal operation will be successful

Amputation through the lower leg would appear offhand to be a more reasonable procedure rather than a low thigh amputation because it would preserve the knee joint However experience has shown that in general it is not a satisfactory type of amputation because of technical difficulties arising from the attachment of muscles in the lower leg and because of the relative paucity of skin and subcutaneous fat with which to fashion a suitable stump Furthermore the prosthesis is difficult for the average patient to manage Amputations through the low thigh may be made either at the supracondylar level which is usually more suitable or through the condyles preserving the patella as a weight bearing surface (Gritti Stokes operation) The Gritti Stokes procedure is more difficult technically and more trouble may be encountered in the healing of the wound it should be reserved for younger individuals particularly men who are engaged in occupations requiring standing on the feet during most of the day Amputations should never be made through the mid thigh unless absolutely necessary

Operations upon the lower extremities can be carried out satisfactorily under low spinal anesthesia Even elderly patients in relatively poor physical condition usually withstand the anesthesia and operation surprisingly well Shock of significant degree during and following the operation is rare Results in this regard are so good as to make unnecessary other forms of anesthesia such as that by refrigeration[8] which have been proposed As a matter of fact among 390 major amputations at the New England Deaconess Hospital Boston from 194- to 1950 the mortality was only 5 8 per cent (Pratt[1,4]) During this same period there were 733 minor amputations (including -7- transmetatarsals) with 3 deaths a mortality of 0 4 per cent The combined major and minor amputation mortality was - 3 per cent

Before and following operation care should be taken to prevent the occurrence of bedsores To this end rubber draw sheets customarily used in hospital beds should be removed The bed should be provided with a Balkan frame or its equivalent using a trapeze or handholds to allow the patient to move himself about in bed It is often desirable to protect the unaffected foot by means of a woolen bed sock and to keep the heel off the bed by placing a small hard hair pillow beneath the lower leg at the level of the Achilles tendon The length of time required in bed following operation varies greatly depending upon the original lesion and the nature of the operation Patients with a low thigh or other amputation in which primary closure is possible may be

allowed up in a chair within 10 to 14 days and may start walking shortly afterward While in the hospital the patient, who has had a low thigh amputation, should be fitted with a temporary prosthesis and taught how to use it Many patients find the relatively light "peg leg" easy to handle and continue with it indefinitely Others, and particularly those in the younger age group, will need after several weeks a permanent type of prosthesis which resembles more closely a natural extremity

There is still all too common a tendency to allow elderly patients to continue with a gangrenous toe or foot over weeks and even months of time in the vain hope that conservative treatment may bring about recovery It is the duty of the physician to evaluate the situation and estimate the prognosis as accurately as he can and then to advise the patient and family as to the most reasonable course keeping in mind the over-all picture A study some years ago showed that, among a group of 166 patients with gangrene, 100 were dead within 3 years from the time of onset of gangrene Among 206 patients, who recovered from amputations of toes or legs carried out because of gangrene the duration of life following operation averaged only 2 9 years In almost every case death took place from manifestations of arteriosclerosis peripheral gangrene, coronary occlusion or cerebral hemorrhage With this in mind it is illogical to carry out a program of conservative therapy over months of time during which the patient is incapacitated and suffering and may face surgery after all at the end of the period Fortunately as has already been discussed in recent years in many of these patients it has been proved possible to carry out the less drastic trans metatarsal amputation

Before the introduction of penicillin and other antibiotics it was not uncommon to be obliged to carry out as an emergency, life saving measure guillotine amputation through the lower leg in patients with infection and gangrene of the foot with ascending lymphangitis Then some days later a definitive low thigh amputation was done With antibiotics such operations have become a rarity because it is almost always possible to check a spreading infection

Medical Management of Surgical Cases—In perhaps no other field of medicine is it so important that the internist and various surgical specialists work closely together for the good of the patient The wards in which such patients are housed have been truly spoken of as "border line wards between medicine and surgery" Whatever the local situation in a given hospital arrangements should be made so that patients are easily accessible day in and day out both to internist and surgeon

Except in emergencies operations should be deferred long enough to allow time to bring the diabetic condition under control However in conditions of extreme urgency it may be necessary to carry out surgery almost at once or after only a few hours of waiting In this situation by careful supervision and planning the diabetic condition can be regulated adequately at the same time that operative procedures are carried out In preparing a diabetic individual for surgery one should have in mind not merely control of hyperglycemia and glycosuria but also hydration of the patient and the provision of a diet as nearly adequate in all respects as complicating conditions will permit On the morning of operation provided the diabetic condition is under satisfactory control food and insulin may simply be omitted until surgery has been completed provided the operation is scheduled at an early hour in the morning and the diabetic condition is not severe Following operation the usual dose of insulin and food or intravenous glucose are given In patients with more severe diabetes whose insulin requirement is larger and particularly if the operation has been scheduled for the late forenoon or the afternoon it is best to give approximately half of the usual dose of insulin at the customary hour before breakfast and to infuse 1 000 c c of 5 per cent glucose in water or salt solution intravenously Following the operation the other half of the usual insulin dose is given and food and fluids administered either orally or parenterally as dictated by the nature of the surgery and the condition of the patient following return from the operating room Usually by thus providing in divided dosage the full amount of insulin customarily taken no further insulin need be given until the following morning when its administration in the usual amount is resumed At times it may be necessary on the day of operation to give one additional dose of crystalline or regular insulin in the late afternoon depending upon the urine test for sugar at that time and less commonly other doses of rapidly acting insulin may be needed

Certain clinicians follow a policy of discontinuing protamine zinc or NPH insulin on the day of operation and for a few days following surgery According to this plan the diabetic condition is controlled by giving regular or crystalline insulin at 3 or 4 hourly intervals depending upon the results of urine tests for sugar carried out through the 24 hours The writer believes however that patients do better if the basic dose of protamine zinc or NPH insulin is continued as already outlined

Coronary Heart Disease

Reference has been made repeatedly in this discussion to the high incidence of arteriosclerosis as a late complication of diabetes. A great deal has been said regarding these degenerative complications in individuals with onset of diabetes under the age of 15 who have survived the disease for 15 [illegible]0 or more years. One does not wish to leave the impression that it is only in erstwhile children with diabetes that one sees striking evidence of premature arteriosclerosis. As nearly as one can tell the same influences are at work in older diabetics which of course constitute the bulk of patients affected by this disease. Mention has been made that in the period from 1944-1949 among [illegible],[illegible]99 deaths among patients of the George F. Baker Clinic there were 1,596 or 69.4 per cent which were due to arteriosclerotic complications. Listed below are the various types of involvement which were responsible for death in these patients.

	Deaths	Per Cent
Heart disease	1,054	45.8
Cerebral vascular disease	269	11.7
Nephritis	161	7.0
Gangrene	71	3.1
Site unassigned	41	1.8
Total arteriosclerotic deaths	1,596	69.4

It is obvious from the preceding figures that deaths due to coronary heart disease head the list, taking a toll 4 times as great as the next most common cause, that of cerebral vascular disease. In a study of autopsy protocols of 349 diabetic patients and 3,400 non-diabetic patients Root, Bland, Gordon and White[86] found coronary occlusion to be 5 times as common in diabetic patients as in non-diabetics of comparable age and sex. In 110 autopsies of diabetic patients dying at the New England Deaconess Hospital between 1940 to 1946 coronary arteriosclerosis was noted in 108 cases by Millard and Root[87]. In contrast to coronary heart disease other types of heart disease in diabetics are relatively uncommon and not of importance in mortality statistics.

There can be no doubt that angina pectoris and coronary sclerosis are more common in diabetics that non-diabetics. It seems definite furthermore that the extent and severity of coronary sclerosis is in

general related to the duration of diabetes as is the case with arterio-sclerotic complications in general Coronary heart disease is more than twice as common among diabetics with hypertension as among those with normal blood pressure In this connection it must be kept in mind that hypertension itself is more common in diabetics than in non diabetics

The treatment of the diabetic patient with angina pectoris and coronary heart disease does not differ appreciably from that of the non diabetic In each group treatment must include limitation of activity appropriate to the individual avoidance in so far as possible of inciting factors trial of medication such as xanthine derivatives and barbiturates to lessen coronary spasm and the use of nitroglycerine for emergencies Diabetic patients with angina pectoris as well as those with peripheral vascular disease will do well to avoid tobacco entirely

An unwarranted fear exists regarding the use of insulin in the treatment of diabetics with coronary heart disease It is obvious that one must use good judgment and common sense in the regulation of the insulin dose but experience has shown that if care is taken it is entirely possible to give without harm and certainly with much benefit doses of insulin which are necessary to maintain good control of diabetes One takes great pains to avoid hypoglycemia but this should by no means be taken to imply lack of adequate control of hyperglycemia and glycosuria

Chronic Nephritis

Justifiable criticism might be made regarding the inclusion of chronic nephritis as one manifestation of degenerative vascular disease since certain types such as pyelonephritis have as their primary cause influences other than vascular However to take up chronic nephritis as a whole at this point seems valid for the sake of unifying discussion and because in the chronic nephritis of the diabetic vascular disease plays such an important role Not infrequently at autopsy two or more forms of renal disease are found to be present and it may be impossible to state which form was primary or more important

Although chronic nephritis as a cause of death among adult diabetics is less important that coronary heart disease varying degrees of nephritis are common In a study of postmortem findings in 110 diabetic patients 59 females and 51 males dying at the New England Deaconess Hospital

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Boston, from 1940 through 1945, Millard and Root[87] found the following incidence of significant renal disease

Chronic Nephritis Type	Principal Cause of Death Number	Associated Finding Number
Intercapillary glomerulosclerosis	2	3
Arteriolarsclerotic	6	29
Glomerular	1	[illegible]
Pyelonephritis	3	18
Total	12	5[illegible]

Allowing for those patients who had more than one form of nephritis in 57 cases or [illegible] per cent of the total definite signs of renal disease were apparent to the pathologist In only 5 cases was the chief type of kidney change that of intercapillary glomerulosclerosis In an additional 10 cases, however, well marked lesions of this form were present making its frequency amount to 14 per cent of the total

Among patients with onset of diabetes in childhood chronic nephritis is at the present time the most frequent cause of death Among 135 deaths of patients in 1944-1949 with onset of diabetes at the age of 15 years or under 70 or 51 9 per cent were due to chronic nephritis Albuminuria and signs of diminished kidney function may appear at any time but only rarely before 10 or 12 years of diabetes have elapsed

In the erstwhile children a now familiar syndrome has been seen all too frequently After 10 to 15 or more years of diabetes proteinuria appears and a tendency to edema at first slight and intermittent occurs General examination may disclose retinitis with fine hemorrhages and waxy exudates increased capillary fragility and calcification of peripheral arteries visible by x ray With progression of the process proteinuria increases the kidney function diminishes the blood non protein nitrogen tends to be elevated retinitis with impairment of vision progresses and an increase in the blood pressure takes place The serum protein becomes low, and there is a tendency to, if not an actual reversal of the albumin globulin ratio The tendency to generalized edema increases with, at times, the appearance of ascites and hydrothorax Although treatment, as discussed later on, may bring about

temporary improvement the course is progressively for the worse and death takes place usually in uremia or congestive heart failure a few years after the onset of handicapping symptoms. In the series of Mann, Gardner and Root[4] the average duration of life after the appearance of any signs of renal disease was 6.4 years with a range of from [illegible] to [illegible] years. In a high percentage of such patients examination of the kidneys at postmortem shows the characteristic lesion to be that of intercapillary glomerulosclerosis.

Although the occurrence of chronic nephritis in young adults as just described is impressive, actually the number of individuals concerned is not great. However, as already mentioned, chronic nephritis of varying degress is not uncommon among the great mass of diabetic patients who are in middle and late life. Indeed, up until recently the cases of intercapillary glomerulosclerosis reported in the literature have been almost entirely in older persons. Thus Kimmelstiel and Porter[55] state that the "nodular" or severe form of this lesion, found in approximately 17 per cent of all cases of diabetes, occurs most frequently during the sixth decade of life.

Diabetics seem peculiarly susceptible to pyelonephritis. Robbins and Tucker[56] stated that this form of renal disease accounted for 1 of 301 deaths. Among the 110 patients of Millard and Root already referred to there were 13 who had active pyelonephritis at autopsy and in 3 of these this was the principal cause of death. In 8 other patients healed pyelonephritis was found by the pathologist.

Treatment.—The treatment of chronic nephritis in diabetics does not differ appreciably from that in non-diabetics. Patients with milder degrees of renal impairment may carry on for years with careful control of the diabetic condition and attention to matters of general health. An adequate protein intake should be provided and in those patients with a low serum protein the amount allowed for an adult should be as much as 100 to 150 grams or more a day if tolerated. Particularly in patients with edema or a tendency to such the diet should be made low in sodium. It is well in such patients that the physician be thorough in making attempts to limit sodium by outlining to the patient in detail which foods are preferable. Salt-free butter and salt-free bread should be provided. Fortunately there are now available newer salt substitutes which contain little or no sodium. The giving of ammonium chloride intermittently in dosage of 4 or more grams a day helps in the excretion of sodium in the urine. In patients with edema diuresis and excretion of unwanted water usually may be stimulated dramatically by the use of

mercurial diuretics given intravenously or intramuscularly Although one must proceed cautiously, experience has shown that even in patients with marked renal impairment such diuretics often may be used with apparent safety and certainly with great comfort to the patient In an attempt to raise the level of plasma protein whole blood plasma or salt free human albumin may be administered intravenously Accessory medication with such patients includes liberal vitamin supplements, inorganic iron such as ferrous sulfate to combat anemia and digitalis, if cardiac decompensation is an accompanying factor in the illness Despite all of the above the ultimate prognosis in such patients with progressive kidney disease *is poor and no therapeutic* efforts available to date have seemed to check the course of the disease appreciably

Cerebral Vascular Disease

Cerebral hemorrhage and thrombosis do not seem to occur with any greater frequency in diabetic than in non diabetic persons although it is true that such vascular accidents accounted for 11 7 per cent of 2,?99 deaths among diabetics in the period 1944-1949 The treatment is the same as in the non-diabetic with due allowance for need of control of the diabetic condition

Not infrequently unconscious diabetic patients are referred to the hospital with the diagnosis of diabetic coma whereas in reality acidosis of significant degree is not present but the condition is due to a cerebral accident However, in such cases the history age of the patient the character of the respiration the absence of dehydration the presence of paralyses reflex changes etc together with results of tests of blood and urine will permit ready decision as to diagnosis and treatment

Diabetic Neuropathy

Among the complications of diabetes diabetic neuropathy ranks high The word neuropathy is chosen with thought to indicate that the involvement of the nervous system is general and not confined to the peripheral nerves It is difficult to give any reliable figure as to the incidence of neuropathy or neuritis since all gradations of severity of the condition are seen Aches and pains are common among diabetic patients and the discomfort from diabetic neuropathy must be differ

entiated from that due to other conditions For a detailed discussion see the articles by Jordan[*] Rundles[*1] and Treusch[*]

The usual diabetic neuritis is a peripheral neuritis involving sensory and at times motor nerves to the extremities usually the legs Following a study of patients at the George F Baker Clinic Jordan classified such neuritis as follows

(1) *Hyperglycemic Type*—Patients in this group usually have no physical signs except tenderness of muscles or nerves affected Such patients have poorly controlled diabetes with hyperglycemia and the pain tenderness numbness and tingling disappear completely within a few or several days after the diabetic condition has been brought under control It seems reasonable that patients if untreated would eventually develop a true neuropathy

( ) *Degenerative and Circulatory Types*—This group includes patients with relatively mild neuritic signs and symptoms which begin insidiously and tend to progress slowly over a period of years Decreased or absent tendon reflexes are common Well marked circulatory deficiency of the legs exists and intermittent claudication may be present

(3) *True Diabetic Neuritis*—In true diabetic neuritis the outstanding symptom is pain down the legs characteristically worse at night Numbness and tingling usually are present and hyperesthesia is often so marked that the pressure even of bed clothing causes pain Muscle weakness of varying degree is present in a high percentage of cases and even complete paralysis in a given muscle or muscle group may be present Examination of the spinal fluid shows an increase in total protein which may be well marked but without increase in the number of cells

The prognosis in diabetic neuritis of the type just described is good If the diabetic condition is maintained under careful control and if an adequate diet is supplied recovery slowly takes place although weeks months and even years may be required The giving of vitamins and particularly of vitamin B complex in large amounts is indicated but rarely does one see dramatic benefit following such

It is believed that the cause of diabetic neuropathy including diabetic neuritis is poorly controlled diabetes Sometimes one is misled by the fact that when the patient actually presents himself for treatment the diabetic condition is under satisfactory control However almost invariably close questioning will reveal that there was a long period of weeks or months of poor control in the more distant past Then as

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sy mptoms of neuritis appeared and progressed, the patient on his own became more careful in treatment and so actually had satisfactorily controlled diabetes when he finally came to the physician The lack of specific or dramatic response to the giving of large amounts of vitamin B complex suggests that the disorder is not basically due to vitamin lack although one cannot deny that this may play a part Some have considered diabetic neuropathy as arteriosclerotic in origin However, in the typical neuritis often seen in young adults it does not seem logical to incriminate arteriosclerosis, since the condition is almost invariably reversible

Diminished Cutaneous Sensation —A high percentage of diabetic patients in middle or late life even in the absence of pain and paresthesia show objective findings of neuropathy including diminished sensation to pinprick and diminished vibratory sense This may be accompanied by diminution or loss of deep tendon reflexes

It is largely because of this diminished sensation so frequently seen that patients must be warned against the use of hot water bottles, electric pads and other agents, thermal chemical and mechanical which may produce injury to the feet In Table XIX rules for the care of the feet have been outlined in detail Diminished sensation is seen both in patients with poor circulation and those with adequate circulation As practical results one sees (a) patients who injure their feet with little or no consciousness of such (b) those who remain on their feet at work with infected lesions which in the non diabetic would cause great pain, (c) those with whom the surgeon is able to carry out, with little or no discomfort, procedures which would cause great pain in the average person A patient seen in the New England Deaconess Hospital afforded the most striking example of the last-named finding This patient, a man 60 years old entered the hospital with infection of the right foot Examination showed insensitivity to pinprick and x-ray revealed the early changes of "neuropathic foot" (see next section) Following subsidence of the infection a transmetatarsal amputation through the foot was carried out by Dr C C Franseen without any anesthesia whatever spinal local or otherwise and the patient said he felt no pain

Neuropathic Foot —One of the rarer manifestations of neuropathy in diabetes is that of the so called neuropathic foot" This condition occurs in patients with other evidences of neuropathy including peripheral neuritis and usually a definite elevation in the spinal fluid protein without increase in cells The earliest gross change seen in the foot is a thickening of the tarsal region which tends to progress slowly and

eventually to produce a thickened deformed foot with tendency to eversion external rotation and flattening of the longitudinal arch The appearance in x rays is quite similar to the Charcot joint of syphilis except that the destruction usually is limited to the tarsal and proximal ends of the metatarsal bones Examination of one such foot by the pathologist showed a complete loss of normal bone structure with numerous spicules of bone scattered throughout the area of involvement undergoing various stages of absorption with an attempt on the part of the remaining periosteum to form new bone In the series reported by Bailey and Root[93] there were 8 males and 10 females with an average age of 56 at the time the foot lesion was discovered (oldest 69 years and youngest 30 years) Diabetes had been present an average of 11 years

Treatment is unsatisfactory and the prognosis poor No case has shown any tendency to improve and the only measure that has proved helpful is the use of orthopedic appliances in an attempt to lessen the trauma of weight bearing and thereby to help prevent further deformity

Paresis of Urinary Bladder—Another rare yet important manifestation of diabetic neuropathy is paresis of the urinary bladder or diabetic cord bladder[90 91] The condition usually is associated with other evidences of neuropathy including neuritic pains paresthesias reflex changes and elevation of the spinal fluid protein without an increase in cells The condition may occur in both young and old but is encountered most often in elderly women Treatment is unsatisfactory although in younger patients return of bladder function may take place if careful control of diabetes is maintained over a long period of time The diet should be adequate in all respects and supplements of vitamin B complex in large dosage should be given As regards the local condition treatment usually has consisted of closed bladder drainage with provision frequently for trials of spontaneous voiding Parasympathetic stimulators such as mecholyl and doryl may be helpful As might be anticipated secondary infection of the urinary tract almost invariably occurs so that in the average case it is desirable to use sulfadiazine or antibiotics in appropriate dosage both in prophylaxis and treatment

Diabetic Nocturnal Diarrhea—Although its exact status is not clear it is possible that the otherwise unexplained chronic diarrhea occasionally encountered in diabetic patients is a manifestation of diabetic neuropathy Characteristically diarrhea occurs in these patients chiefly or entirely at night and in more than three fourths of the 40 patients reported by Sheridan and Bailey[94] there was nocturnal incontinence of

feces The condition usually is intermittent with remissions lasting for several days followed by a relapse In the series of Sheridan and Bailey there were 23 males and 17 females with an average duration of diabetes of 9 years The age of the patient at onset of diarrhea varied from 17 to 29 years X-rays of the gastrointestinal tract were negative in all patients except for increased spasticity of the colon noted in 6 of the 40 patients Only 14 of 29 patients tested had absence of free hydrochloric acid in the gastric contents In each of the 40 cases there was evidence of poor control of diabetes prior to onset of the diarrhea, and in 23 cases peripheral neuritis preceded the diarrhea In 17 of 18 cases studied there was a definite increase in the spinal fluid protein

Treatment of the diarrhea in this group of patients is most difficult A low residue non irritating diet with vitamin supplements particularly of the vitamin B complex should be prescribed The giving of hydrochloric acid sulfonamides and drugs exerting a costive effect is of little benefit but should be tried In some patients the administration of crude liver extract intramuscularly in dosage of 2 to 4 c c daily for a few days followed by a maintenance dose of 1 to 2 c c weekly, has appeared to benefit more patients than any other procedure Usually, however, treatment has had to be carried out over a period of weeks and months In some it has appeared that lapses in treatment have been followed by relapses of diarrhea

Infections

The individual with poorly controlled diabetes is unusually susceptible to infections particularly to tuberculosis and to infections of the skin and urinary tract However the outlook for the diabetic in this regard has improved greatly in recent years First, with insulins of prolonged action it is now possible to obtain better and more continuous control of the diabetic condition than ever before and thereby increase resistance to infection Second the sulfonamides and the antibiotics penicillin and streptomycin have increased greatly chances of success in treating infections once established Nevertheless infections still constitute a menace and usually increase the insulin requirement temporarily During infections tests of urine for sugar must be made more frequently than usual and the insulin dosage adjusted to provide satisfactory control The diet must be altered to suit the condition of the patient (see Table XI)

Infections of the Skin — Infections of the skin are not uncommon in diabetic patients *particularly if the disease is poorly controlled* From the very outset of treatment patients should be instructed carefully as to the need for cleanliness of the skin including that of the feet Skin infections vary from small furuncles to boils and huge carbuncles The smallest lesion deserves attention because usually carbuncles have their origins in minor lesions

A carbuncle may occur anywhere over the body but is seen most commonly on the back of the neck and particularly in men Formerly it was one of the most serious complications seen in diabetics and even today deserves most careful respect and attention However with this as well as with other infections in the diabetic penicillin and other antibiotics have conferred a great blessing and have altered the plan of treatment radically[49] Before their advent the most successful program of therapy included localization of the infection by means of frequent applications of moist hot dressings or poultices with radical crucial incision and drainage at an appropriate time It was found that localization could be hastened often by x ray therapy At present when the patient with a boil or carbuncle is seen first he should be started on penicillin at once in dosage of 60 000 to 100 000 units every three hours This may be combined with hot compresses locally The experience to date has been that large amounts of penicillin frequently will bring about remarkable subsidence and diminution in size of the lesion At times in cases obtained early no surgery at all may be necessary In patients seen first with the infection at a more advanced stage antibiotic treatment usually will result in decrease of the indurated inflammatory area and localization of purulent material to a much smaller lesion than heretofore possible The result is that incisions are smaller and the period of incapacity greatly lessened It goes without saying that the diabetic condition should be carefully controlled by means of adequate amounts of insulin

A further word is necessary regarding the crucial incision which may still be necessary in certain patients despite penicillin therapy This incision should be extended until sound tissue is reached sloughing material should be cut away and large gauze packs placed under the skin flaps In subsequent dressings the careful application of Dakin s solution to keep the packs moist helps to clear away necrotic tissue (the surrounding skin should be protected as with tincture of benzoin to prevent irritation) Following drainage of the carbuncle the greatest

care should be taken to prevent the contamination of surrounding healthy skin and the formation of satellite infections

Genitourinary Tract—The well known susceptibility of the diabetic to infections extends to the urinary tract This is illustrated in the fact that at the George F Baker Clinic of 212 deaths among diabetics from 1939 1945 there were 40 patients or 19 per cent with genito urinary disease This agrees closely with a figure obtained with a larger series of 422 autopsies done between 1919 and 1945 in which infection of the genitourinary tract was found in 85 cases or 20 per cent Infections are most likely to take the form of cystitis pyelonephritis, para nephric abscess prostatic abscess and hypertrophy of the prostate with accompanying urinary tract infection The diabetic with an infection of the urinary tract today has a great advantage over his counterpart of three decades ago Now it is possible not only to raise his resistance to infection by means of careful control of diabetes with an adequate diet and insulin but also to treat him with powerful bacteriostatic and bactericidal agents such as the sulfonamides and antibiotics It is, of course imperative that the organism causing the infection be identified so that the proper therapeutic agent can be selected If as is often the case the organism is *E coli* success may follow the use of sulfadiazine or other sulfonamides even in relatively small doses such as 2 grams a day If these measures fail, or if the organism isolated is such that no response to sulfonamides might be anticipated then antibiotics including penicillin streptomycin aureomycin, chloromycetin and terramycin should be considered In the matter of the choice of the antibiotic to use, it is desirable to carry out in vitro tests to determine the sensitivity of the organism to the particular agent under consideration

It must be admitted that absolute eradication of infection in the urinary tract of diabetic patients and particularly in middle aged and elderly women is often a most difficult problem In the absence of symptoms a common sense appraisal of the patient s general condition and life expectancy must be made in order to decide how persevering and drastic one should be in therapeutic endeavors Certainly there must be no delay in investigation of pyuria and treatment must be thorough Destructive changes may occur within a few weeks time changing a reversible to an irreversible condition Distention of the bladder should be avoided particularly in elderly patients and in those in coma and following operation Although one should not catheterize patients needlessly or without careful thought failure to do so may do more harm

than not After catheterization . grams of sulfadiazine may be given daily for a few or several days as a prophylactic against infection

Tuberculosis—Statistics prior to the introduction of insulin showed an extremely high incidence of tuberculous infection in diabetics Prior to 1900 pulmonary tuberculosis was found in nearly 50 per cent of autopsies performed on diabetic patients in public hospitals in large cities of Europe These figures of course reflected the widespread prevalence of tuberculosis among the general population With increasingly greater adoption of modern public health measures tuberculosis has become less frequent and this is true also among diabetics Furthermore diabetics themselves are benefited by the improved health and increased resistance to infection brought about by better control of diabetes made possible with insulin

In the George F Baker Clinic from 1898 19 2 4 9 per cent of deaths among diabetics were due to tuberculosis In the period 19 1936 the percentage was 4 2 but this fell subsequently so that in the most recent period tabulated from 1944 1949 of 99 deaths only 2 1 per cent were due to tuberculosis Not so heartening is the fact that of 135 patients with onset of diabetes under the age of 15 years and dying in 1944 1949 15 or 11 per cent died of tuberculosis (Joslin and Wilson[151])

In the treatment of diabetic patients with tuberculosis the diet must be made liberal enough in calories and in protein mineral and vitamin content to permit satisfactory maintenance of weight and strength Insulin should be prescribed in dosage adequate to insure excellent control of hyperglycemia and glycosuria The principles regarding the use of pneumothorax and surgical measures are the same as for non diabetics Experience has shown that such patients may successfully withstand major lung surgery such as lobectomy or pneumonectomy

The early detection of tuberculosis both in the diabetic and the non diabetic population depends in large part on routine x rays of the chest periodically The proposal to take such x rays routinely at the time of admission to hospitals is sound

Complications Affecting The Skin

Infections of the Skin—(see under Infections on a previous page)

Necrobiosis Lipoidica Diabeticorum—An unusual condition occurring chiefly though not exclusively in diabetic persons is necrobiosis lipoidica diabeticorum[8] The earliest lesions are elevated red papules from 1 to 3 mm in diameter with sharply outlined borders They may

care should be taken to prevent the contamination of surrounding healthy skin and the formation of satellite infections

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condition so as to bring about lowering of blood lipid and cholesterol values When this is accomplished by means of diet and insulin the lesions disappear

Similar xanthomatous lesions xanthomata tuberosa and plana occur as evidence of a systemic disease primary xanthomatosis in which not only the skin but also the viscera are involved Xanthomata tuberosa and plana are associated with an increase in cholesterol total fat and monoaminophosphatid content of the blood serum In this condition both blood and skin abnormalities tend to persist For more extensive discussion of xanthoma see Chapt XII A Vol IV

Complications Involving the Digestive System

Complications involving the gastrointestinal tract are not uncommon in patients with diabetes and may or may not be related to the disease itself

Mouth and Teeth—Aside from the dryness of the tongue and mucous membranes of the mouth the swelling and purplish discoloration of the gums and looseness of the teeth which may be encountered in diabetic acidosis and coma there are no characteristic oral findings in diabetes It is true that the mouth and teeth of diabetic patients are often in poor condition but surveys of the general population have shown this to be true among people at large The usual cause is neglect in daily care of the teeth and gums at home and failure to seek dental advice and treatment at regular intervals It is encouraging to find that there are many young diabetic patients who are comparatively free from dental disease In a study of 43 patients from 11 to 25 years of age with diabetes of 10 to 20 years duration Kent[8] found 18 patients with no fillings or cavities and in the entire group only 10 teeth including 1 third molars had been extracted Kent believes that juvenile diabetics have teeth which are in as good or better condition than those in non diabetic individuals in the same age group Kent states however that if the onset of diabetes occurs during the middle and latter part of the high caries susceptibility period between the ages of 7 and 10 and particularly if diabetes is poorly controlled during this time the incidence of carious and infected teeth is great

In planning the diet of the diabetic particularly the growing child care must be taken to insure an adequate vitamin and mineral intake Every juvenile diabetic should receive in his diet at least one gram of

be capped by a slight scale and do not disappear under pressure In later stages the lesions take the form of round oval or irregularly shaped plaques with well-defined borders having a firm consistency and glisten ing surface Still later there may occur a circular area of depression with atrophy and ulceration With care to prevent secondary infection, almost invariably the shallow ulcerations eventually fill in, leaving a thin layer of scar tissue

Necrobiosis lipoidica diabeticorum occurs most commonly in young diabetics in -5 patients with this lesion the average age of onset of diabetes was 17 7 years It occurs more commonly in females than in males In some patients a history of injury may be obtained The lesions may be single or multiple and they occur most often on the lower legs or about the ankles At times surprisingly symmetrical lesions may occur on the two legs

The etiology of this peculiar skin condition is unknown as possible causes have been mentioned endarteritis fatty degeneration or necrobiosis of connective tissue and localized arteriosclerosis No specific treatment is available The diabetic condition should be controlled carefully and standard local treatment of the lesions provided if they become ulcerated or secondarily infected

Xanthochroma—Xanthochromia or xanthosis is a yellowish discoloration of the skin seen at times in diabetic patients It is particularly noticeable on the palms of the hands, soles of the feet and on the nasolabial folds It is accompanied by an increase in the carotin content of the blood and often of the cholesterol content as well It is due to a disturbance in the patient's ability to metabolize carotin which is found in large amounts in green vegetables egg yolk carrots and butter Xanthochromia is not confined to diabetics Treatment consists in adequate control of the diabetic condition temporary restriction of the intake of carotin rich foods and supplementary medication with vitamins and minerals as indicated to replace those ordinarily supplied by the foods restricted

Xanthomata—A now uncommon skin condition in diabetic patients is that of xanthoma diabeticorum in which are seen scattered bright red nodules mottled with a deep rose tint The individual lesions vary in size some having a diameter as great as 5 mm The lesions are most numerous on the outside and back of the forearms and especially about the elbows and knees In patients with diabetes they are associated with an increase in the total lipid and cholesterol content of the blood to which they are secondary Treatment consists of control of the diabetic

diseases It is obvious that appropriate studies must be carried out to ascertain whether or not the diarrhea is due to causes as these There has been considerable discussion in the past regarding the possible role of achlorhydria or impaired external secretion of the pancreas in the causation of diarrhea in diabetics As regards the former it is true that absence of free hydrochloric acid may be found in certain diabetic patients but the best evidence suggests that only occasionally may there be a causal relationship Actually the only evidence for such relationship lies in the fact that at times the administration of dilute hydrochloric acid is followed by improvement Likewise only rarely is there any good evidence that the external secretions of the pancreas are impaired to the extent that diarrhea results For a discussion of diabetic nocturnal diarrhea see a preceding page

Vomiting —Vomiting is a symptom which always demands respect in a diabetic patient It is an almost invariable accompaniment of diabetic acidosis and coma and as such may be a warning sign which calls attention to a serious complication demanding early and energetic treatment Strangely enough occasionally nausea and uncommonly vomiting may be symptoms of the exactly opposite condition that of hypoglycemia due to insulin and particularly to protamine zinc insulin Relief comes with elevation of the blood sugar to a satisfactory level

In patients who are vomiting for reasons apart from diabetes it may be necessary to give food and fluid parenterally for periods varying from a matter of hours to days When such a situation arises glucose should be given intravenously or subcutaneously in amounts large enough to provide at least 100 and preferably 150 grams of carbohydrate in 4 hours As to whether or not the infusion should contain sodium chloride also depends upon the condition and needs of the patient concerned If parenteral feedings are to be continued over a matter of days then the physician does well to include not only glucose but also amino acid preparations so that the protein requirement may be at least partly satisfied Likewise supplementary vitamins particularly B complex and C should be given parenterally in adequate dosage During periods of nausea and vomiting a basic dose of protamine zinc insulin with or without regular or crystalline insulin should be continued and supplementary doses of unmodified insulin given at other times during the 4 hours as indicated by urine tests for sugar

Gastric and Duodenal Ulcer —Gastric and duodenal ulcers occur in diabetics with about the same frequency as in non diabetics when due allowance is made for the fact that diabetes occurs most commonly in

calcium a day Furthermore the diabetic condition must be controlled as carefully as possible and the patient must be taught how to give proper local care of his teeth and gums

For the extraction of teeth the following rules have proved sound

(1) The diabetic condition must be under satisfactory control

(2) Particularly if infection and pyorrhea are present no more than 2 or 3 teeth should be extracted at a sitting

(3) Local anesthesia as with novocain is desirable since its use does not interfere with the diabetic regime of diet and insulin

(4) Particularly in patients with infected teeth, one may to advantage give penicillin preceding and following extraction

Constipation —Constipation is probably as common among middle aged and elderly diabetic patients as it is among people of similar age in the general population This is somewhat surprising since the average diabetic diet is liberal in fruit and vegetables By the choice of laxative fruit by daily exercise by liberal intake of fluids and by regular bowel habits the patient should attempt to correct the condition without the use of drugs With proper cooperation on the part of the patient a laxative habit of many years' standing can be broken at times in a relatively short period of time by common sense application of the above measures However in many cases this is not possible and resort must be had to drugs using those laxatives least likely to cause harm Standard laxatives such as cascara rhubarb, milk of magnesia and saline preparations are allowable Formerly one gave without hesitation doses of mineral oil of varying size and often patients took this preparation in astonishingly large amounts Evidence has accumulated recently to indicate that the presence of mineral oil in the bowel may prevent the absorption of important amounts of vitamin A and thereby lead to vitamin deficiency hence its frequent use should be discouraged

Diarrhea is an unpleasant symptom in any person and assumes more than usual importance in the diabetic It may have various causes Prior to the introduction of insulin it apparently followed the use of a bulky diet with an overabundance of green vegetables and rough foods This type of difficulty is usually not encountered at the present time and if so the giving of a concentrated diet with the temporary exclusion of bulky vegetables and laxative fruits will correct the difficulty However diarrhea in a diabetic patient may not have a simple cause and may not be easily overcome It may be due to some condition entirely unrelated to diabetes such as amebic or bacillary dysentery mucous or ulcerative colitis carcinoma of the lower bowel and other complicating

examination the edge of the liver became soft or difficult to feel when the diabetic condition had been brought under control Although there was a moderate increase in the blood cholesterol there was little or no decrease in the percentage of the ester fraction In the thought that perhaps the enlargement of the liver was due to lack of choline these patients were treated with betaine a chemical relative of choline over periods as long as 8 months No striking change was seen in the size of the liver but at about that point in the investigation protamine insulin and shortly thereafter *protamine zinc insulin were made available* for general use Along with improvement of the general condition of the children the size of the liver diminished markedly in almost all of them and since then has not been an important complication in the juvenile patient It was clear that the enlargement of the liver was due not to lack of choline but to the disturbed metabolism of poorly controlled diabetes It was believed that the hepatomegaly was due primarily to gross fatty infiltration and that a possible contributory factor was hydropic degeneration with water retention

Cirrhosis of the Liver —Cirrhosis of the liver occurs with probably about the same frequency as it does in non diabetic individuals By the use of insulin it is possible to furnish a diet liberal in carbohydrate and protein just as in the non diabetic Other treatment consists in the supplying of large supplements of vitamin B complex the giving of choline and/or methionine the use of crude liver extract parenterally in some patients and resort to surgery such as portal-caval shunt and spleno renal anastomosis in carefully selected cases

Hemochromatosis —A condition allied to cirrhosis of the liver is that of hemochromatosis in which hepatic cirrhosis is due presumably to the reaction of the liver to the retention and deposition of large amounts *of iron* The abnormal *retention of iron is not confined to the liver* by any means but is a generalized process affecting all body tissues In addition to cirrhosis of the liver hemochromatosis is characterized by a brownish or grayish pigmentation of the skin In later stages of the process diabetes may result probably from changes induced in the pancreas because of abnormal deposition of iron in that organ Because of this the condition has been known as bronze diabetes Actually however the presence of diabetes is not essential for the diagnosis of hemochromatosis

Hemochromatosis is an uncommon disease At the time of writing his excellent monograph on this disease in 1935 Sheldon[93] was able to collect from the literature only 311 cases in which the diagnosis seemed

women in middle life and beyond whereas peptic ulcer most commonly occurs in young adult males Treatment does not differ from that used in persons without diabetes

Cholecystitis and Cholelithiasis —It appears likely that gallbladder disease is somewhat more common in diabetic individuals than in persons in the general population Thus in a study of postmortem material Warren found that in persons over 30 years of age gallstones were present in 30 7 per cent of 453 diabetics as compared with an incidence of 21 4 per cent of 55 non diabetics Similarly at the Mayo Clinic in 197 autopsies on diabetic patients between 1919 and 1936 gallstones were present or had been removed at operation in 66 or one third of the patients[97] In a study of 154 patients with diabetes complicated by gall bladder disease Jordan[98] found that the gallbladder disease preceded diabetes twice as often as the reverse was true and the average duration of gallbladder disease prior to the onset of diabetes was 9 years This agrees with common clinical experience and formerly led to the thought that gallbladder disease might be related to diabetes etiologically However the weight of evidence is against this It is possible, however, that the disturbed fat and cholesterol metabolism seen in connection with diabetes may account for the increased incidence of gallstones

Although surgical treatment of gallbladder disease has no more beneficial effect upon the diabetic condition than does the clearing up of any comparable infection in the body gallstones must always be considered a hazard to the diabetic patient, and in general, it is wise to advise their removal at an appropriate time even though they may have been asymptomatic

Enlargement of the liver is not uncommon in diabetic patients but when one compares the weights of livers removed at postmortem examination from diabetics who have been under treatment and non diabetics of comparable ages no noteworthy difference is apparent There can be no doubt, however that enlargement of the liver does occur in poorly controlled severe diabetes This was seen most strikingly in juvenile patients prior to 1937 the year in which protamine zinc insulin was introduced A special study was made of 60 young patients with severe poorly controlled diabetes one third of whom were diabetic dwarfs being 4 inches or more below standard height for age[73] In these patients the liver was truly large with the lower edge of the organ not infrequently in the pelvis In 31 cases or more than one half of the total splenomegaly was present The abdomen usually was enlarged and episodes of abdominal pain were common On physical

examination the edge of the liver became soft or difficult to feel when the diabetic condition had been brought under control Although there was a moderate increase in the blood cholesterol there was little or no decrease in the percentage of the ester fraction In the thought that perhaps the enlargement of the liver was due to lack of choline these patients were treated with betaine a chemical relative of choline over periods as long as 8 months No striking change was seen in the size of the liver, but at about that point in the investigation protamine insulin and shortly thereafter protamine zinc insulin were made available for general use Along with improvement of the general condition of the children the size of the liver diminished markedly in almost all of them and since then has not been an important complication in the juvenile patient It was clear that the enlargement of the liver was due not to lack of choline but to the disturbed metabolism of poorly controlled diabetes It was believed that the hepatomegaly was due primarily to gross fatty infiltration and that a possible contributory factor was hydropic degeneration with water retention

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Hemochromatosis —A condition allied to cirrhosis of the liver is that of hemochromatosis in which hepatic cirrhosis is due presumably to the reaction of the liver to the retention and deposition of large amounts of iron The abnormal retention of iron is not confined to the liver by any means but is a generalized process affecting all body tissues In addition to cirrhosis of the liver hemochromatosis is characterized by a brownish or grayish pigmentation of the skin In later stages of the process diabetes may result probably from changes induced in the pancreas because of abnormal deposition of iron in that organ Because of this the condition has been known as bronze diabetes Actually however the presence of diabetes is not essential for the diagnosis of hemochromatosis

Hemochromatosis is an uncommon disease At the time of writing his excellent monograph on this disease in 1935 Sheldon[13] was able to collect from the literature only 311 cases in which the diagnosis seemed

well-established. Marble and Bailey[8] found 30 cases proven either by autopsy or skin biopsy among approximately 30,000 diabetic patients seen since 1922. The outstanding signs and symptoms among the 30 cases were (1) brownish or grayish brown pigmentation in 24 cases, (2) enlargement of the liver in all cases, (3) enlargement of the spleen in 23 cases, (4) loss of weight and strength in all patients, (5) history of abdominal pain in 11 cases, (6) ascites in 11 cases. The history of diabetes in relatives was obtained in 12 patients. Seven patients took alcohol moderately or excessively, 7 rarely and 16 were abstainers. In addition to the 30 cases Marble and Bailey found 17 others with the classical triad of hepatomegaly, pigmentation of the skin and diabetes with whom it was not possible to prove the diagnosis by skin biopsy. However, it is well recognized that the skin biopsy may be negative and yet large amounts of iron pigment be found in the viscera.

The cause of hemochromatosis is not clear. Mallory's suggestion that it is due to chronic copper poisoning has not received general acceptance. There is no evidence to indicate that the excess of iron is due to excessive hemolysis. A conception now widely held is that hemochromatosis is an "inborn error of metabolism" in which there is a disturbed intracellular circulation of iron. Recent studies by Rath and Finch[103] at the Peter Bent Brigham Hospital in Boston suggest that in hemochromatosis there is abnormal absorption of iron but normal storage of iron in the body. So far these workers have been unable to find any mechanism for excretion of excess iron from the body either in the normal person or in the one with hemochromatosis. They find, except for brief periods following injection, that practically all of the iron in the blood serum is bound to protein and more particularly to the beta globulin fraction. The blood serum has in the normal person a capacity of taking up approximately 300γ of iron per 100 c.c. Under normal circumstances about ⅓ of this binding power is satisfied. In the patient with hemochomatosis the capacity is somewhat less, amounting to about 200γ per liter, and a much higher percentage (90 to 100 per cent.) of this is satisfied. Attempts so far to remove iron from these patients have been successful only by phlebotomy.

The characteristic symptoms of hemochromatosis are loss of weight and strength, increasing pigmentation of the skin, abdominal distress and often impotence. Physical examination reveals usually signs of weight loss, brown or bronze color of the skin, which is more striking on the exposed surfaces, usually an enlarged abdomen in which the liver is large and may be tender, and often the spleen is palpable, and

distention of the superficial veins along the costal margin and over the lower chest. In later stages of the cirrhotic process ascites may be present requiring paracentesis. In men there is often atrophy of the testes and prostate together with scanty axillary and pubic hair. The blood pressure may be low but usually not strikingly so. Hypochromic anemia may be present.

Hemochromatosis is uncommon in women. In Sheldon's 311 cases there were only 13 instances of the disease in females and among the 30 reported by Marble and Bailey there were only three women.

Patients with hemochromatosis may require extraordinarily large amounts of insulin for control of the diabetic condition but a high insulin requirement is by no means a constant finding. Among the 30 patients described by Marble and Bailey the insulin varied from 0 to 1,600 units a day; in 17 of the 30 cases the daily dosage was under 50 units. Only 6 patients ever required more than 100 units in 24 hours.

The diagnosis of hemochromatosis may be suspected by the history and physical findings and by laboratory studies indicating the presence of diabetes. Verification must be made by the demonstration of abnormal amounts of intracellular iron. The best way, other than liver biopsy, is to excise a bit of skin for histological study, using care not to make the biopsy in the axillae or groin or from any other part of the body where normally small amounts of iron pigment may accompany large amounts of melanin. The skin removed should be dropped immediately into 80 per cent alcohol or formalin and the tissue suitably treated for microscopic examination. As an aid in diagnosis one may attempt to demonstrate hemosiderin in epithelial cells of the urinary sediment.[101] To do this a freshly voided sample of urine is centrifuged. The supernatant fluid is discarded and the sediment resuspended in 10 c.c. of a fresh mixture containing equal parts of 2 per cent potassium ferrocyanide and 1 per cent hydrochloric acid. The presence of iron is indicated by intracellular granules which stain blue. In interpreting the test one must take care to differentiate such granules from nondescript deposits of stain which lie on top of or outside cells. A third method of diagnosis in the living patient has been proposed by Fishback.[102] This test consists of the intradermal injection of a small amount of fluid made up of equal parts sterile 0.5 per cent solution of potassium ferrocyanide and N/100 hydrochloric acid. It is stated that if abnormal amounts of iron are present in the skin the wheal will turn a light blue almost immediately and this will darken to a deep blue within five minutes. However, in the hands of the writer and his associates this intradermal test has not

proved helpful and the procedure of skin biopsy has seemed much more reliable. Biopsy of the liver probably is not justifiable unless it is done by puncture or incidentally in the course of a laparotomy performed for some other reason. Finch[100] on the basis of data now available believes that a determination of the iron binding power of the blood serum and the degree of its saturation may prove helpful in diagnosis.

The *treatment* of hemochromatosis prior to the discovery of insulin presented a most difficult problem. At the present time the situation is a great deal better. The diabetic condition can be controlled with insulin and by virtue of this it is possible to provide a truly adequate diet containing a liberal allowance of carbohydrate and protein together with supplements of vitamins, particularly vitamin B complex. The diet for a patient with hemochromatosis may well contain 180 to 200 or more grams of carbohydrate and 100 or more grams of protein. It is likely that rigid restriction of fat is not necessary and indeed may not be desirable so that the amount of this type of food may be adjusted according to the body weight of the patient and his tolerance for fat. Vitamin B may be given either as brewers' yeast or in the form of concentrates. One should not give inorganic iron for an accompanying anemia since available evidence suggests that any iron so given will simply add to the body's unwanted store of this element. The patient with hemochromatosis has ample amounts of iron in his body for the formation of red blood corpuscles, and if anemia exists, the suggestion is strong that there is some inadequacy in the blood forming function of the bone marrow.

With several male patients with hemochromatosis White[8] has shown that in addition to atrophy of the testes and prostate there is a subnormal excretion of 17 ketosteroids in the urine. When these patients were treated with testosterone in dosage of 25 mgm two or three times a week there was in some cases apparent improvement as shown by an increase in strength and improvement in general health. For additional discussion of hemochromatosis see Vol. VIII, Chapt. IV.

Diseases of Endocrine Glands other than the Pancreas

Reference has already been made in the section on "Pathological Physiology" to the importance in diabetes of not only the pancreas but also the other glands of internal secretion, the anterior pituitary, adrenal

cortex thyroid and gonads In the following paragraphs only the clinical aspects of this subject will be touched upon

Pituitary —In the article by Davidoff and Cushing[103] published in 19 7 it was reported that among 100 patients with acromegaly 12 had diabetes Subsequently in a follow up of 153 of Cushing s cases of acro megaly Coggeshall and Root[104] found that 36 per cent had glycosuria and that 17 per cent had true diabetes These findings are certainly significant but one must concede that if there is an etiological relation ship such as one commonly assumes it is surprising that diabetes is not even more common in acromegaly and that acromegaly is so rare in diabetics

It is customary to state that in acromegaly the diabetic condition pursues a wave like course with periods of improvement alternating with those of exacerbation In practice such a course is not common and the treatment of the diabetes of the acromegalic usually is the same as that of any other diabetic patient Although patients with acromegaly and diabetes may be insensitive or resistant to insulin actually this is not often the case

Thyroid —Although experimental and clinical experience indicates that the relationship of the thyroid gland to diabetes is not as close as that of the anterior pituitary the status of thyroid function has a definite bearing upon carbohydrate metabolism In general it may be stated that individuals with hyperthyroidism have a diminished tolerance and those with hypothyroidism an increased tolerance for carbohydrate This relationship seemed so definite to some workers in the recent past that total ablation of the thyroid was carried out in certain patients with diabetes in the hope of ameliorating the disease[105 106] This effect was secured but the results were not striking Furthermore as with total thyroidectomy carried out with disabling heart disease it has appeared unwise to add another chronic disease myxedema to the patients burdens In the experience of Joslin and Lahey[4] in 38 6 per cent of cases of primary hyperthyroidism and in .7 7 per cent of cases of sec ondary hyperthyroidism there was glycosuria Diabetes was present in 2 5 per cent of patients with primary hyperthyroidism and in 4 3 per cent of those with secondary hyperthyroidsim These figures are con sistent with those reported from the Mayo clinic Wilder[97] found the incidence of diabetes to be 3 3 per cent among 1 882 cases of hyper thyroidism seen from 1935 to 1938

Milder degrees of disturbance in carbohydrate metabolism may seem to disappear after subtotal thyroidectomy with relief of hyper-

thyroidism From a practical clinical standpoint one must be cautious and limit the diagnosis of diabetes to those patients in whom the disturbance is well-marked and not likely to disappear after surgery It is the practice of the writer and his associates to make the diagnosis of diabetes in the presence of hyperthyroidism only if the blood sugar following food or glucose rises to a height of 200 mgm per 100 cc or more (venous blood, Folin methods)

The occurrence of thyrotoxicosis in a patient with diabetes usually causes a flare up in the diabetic condition and an increase in the insulin requirement Consequently in any diabetic, who in the past has been progressing satisfactorily who now begins to suffer an increase in hyperglycemia glycosuria and insulin requirement, and who is losing weight and strength, one should keep in mind the possibility of hyper thyroidism

The treatment of hyperthyroidism in the diabetic proceeds along the same lines as that of the non diabetic In the present day satisfactory clinical results usually follow preparation of the patient with propyl thiouracil and iodine followed by subtotal thyroidectomy Rarely following operation thyroid 'storm' may pose a most difficult problem for the clinician In a few such patients in whom thyroid storm and diabetic coma coexisted recovery took place following the use of large amounts of insulin and iodine and salt solution intravenously In the treatment of the diabetic patient following operation usually no special measures are necessary as regards the diabetes except to provide a diet liberal enough to allow return to normal weight and strength

Myxedema or hypothyroidism are uncommon accompaniments of diabetes but the combination does occur Indeed Shepardson and Wever[107], after a study of the problem concluded that the two condi tions occurred together to about the same extent as might be predicted from the occurrence of either disease alone

Adrenal Glands —Mention has been made earlier of the relationship of the adrenal glands to carbohydrate metabolism Clinically one sees experimental observations borne out by the occurrence of glycosuria and diabetes in patients with tumors of the adrenal cortex Cases of pheochromocytoma with diabetes in which the diabetes apparently disappeared following surgical removal of the tumor, have been re ported by Duncan Semans and Howard[108] and by Green[109]

In Addison s disease hypoglycemia is the rule but there are rare instances of the occurrence of diabetes and Addison s disease in the same patient

Genitourinary System

Infections—(see section on Infections)

Calcification of Vas Deferens—An unusual and remarkable condition seen almost exclusively in diabetic patients is that of calcification of the ductus (vas) deferens In such cases one sees in x rays the course of the ductus deferens on either or both sides outlined in whole or in part by deposits of calcium The finding usually is an unexpected one and made on routine examination It often accompanies calcification of arteries Marks and Ham[110] noted the occurrence of this condition in 9 diabetic patients More recently Wilson and Marks (paper to be published) have reported upon 60 patients with calcified vas deferens seen at the New England Deaconess Hospital Of these only 4 were non diabetic despite the fact that during the period of time covered by the survey six times as many non diabetic as diabetic patients were observed

Ocular Complications

Disorders affecting the eyes are common in diabetes Abnormalities range in importance all the way from transient refractive errors to extensive retinitis leading to blindness In addition the diabetic is subject to the same eye complications which affect people in general

Transient Refractive Errors—Transient refractive errors are common in patients in whom there are marked hyperglycemia and glycosuria Indeed blurring of vision due to hyperopia or to diminished myopia may be one of the chief symptoms On the other hand when patients with uncontrolled diabetes are brought under treatment rapidly and the blood sugar level reduced blurring of vision may be noted by an individual who previously had not had this difficulty In this instance the blurring is due to myopia or to lessened hyperopia These refractive changes are bilateral and last from a few days to a few weeks The magnitude of the change usually amounts to 2 diopters or less but at times may be as great as 8 diopters These transient errors are due to changes in the index of refraction of the lens nucleus incident to osmotic shifts Patients should be advised not to have eyeglasses fitted until 3 or 4 weeks of stabilization of the diabetic condition have elapsed

Lipemia retinalis[111] is applied to a striking appearance of the retinal vessels in certain diabetics with hyperlipemia and is seen usually in

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due to diabetic and how much to non diabetic influences However now that persons with onset of diabetes at the age of 15 years and under have been able with the aid of insulin to live 15 20 or more years with diabetes, it has become apparent that retinitis is one of the earliest evidences of vascular disease to become manifest Furthermore since among these erstwhile juvenile diabetics it occurs so frequently and so extensively in an age group in which such abnormalities are uncommon, there can be no doubt that diabetes is the cause There are those, who believe that the vascular damage of retinitis is due not to poorly controlled diabetes but to some unknown factor which would be operative in these individuals even if the diabetes were carefully regulated The writer and his associates do not subscribe to this view It is their belief that such complications would not arise if means were at hand to control the diabetic condition constantly hour after hour and day after day Obviously at the present time this is impossible except under the most unusual conditions Earlier in this discussion data as to the incidence of vascular disease in patients with onset of diabetes in childhood were presented It will be recalled that among 200 patients with onset of diabetes at the age of 15 years or under and who had survived 20 years of the disease 80 per cent were found to have retinal hemorrhages In the same group sclerosis of the retinal arteries was noted in 85 per cent of cases although one must admit that the validity of this figure is not as great as that of the incidence of hemorrhages because the data depend more upon personal interpretation In their study already referred to Waite and Beetham found that characteristic retinal abnormalities were deep retinal hemorrhages and waxy exudates Evidences of diabetic retinopathy increase with increasing duration of diabetes

At the present time is is impossible to state the exact cause of retinopathy in diabetes It may possibly be related to long continued subclinical acidosis There is nothing to suggest that vitamin deficiency plays an important role In some patients retinitis may be correlated with an increase in capillary fragility[114] For this reason rutin has been given to many patients in the last few years, usually now in dosage of 100 mgm three times a day in an attempt to lower the capillary fragility to normal and to arrest the tendency to retinal hemorrhages It has been difficult to acquire conclusive data as to whether the use of rutin is helpful It is a clinical impression that in some patients there has been disappearance of hemorrhages or at least the prevention of new ones However results are not clear cut and in Barnes study[11] of our patients

patients in or recovering from acidosis The vessels appear wide and flattened and are salmon to cream in color, often the arterioles and veins look almost alike In two cases reported by Marble and Smith[11] the total lipid content of the blood was 14 1 and 7 5 per cent respectively There is, however, no close correlation between the level of blood fat and the appearance of lipemia retinalis It seems likely that the physical state of the fat is a factor With adequate treatment of the diabetic condition the level of blood fat falls quickly, and the lipemia retinalis disappears

Wrinkles—A minor but interesting abnormality was pointed out by Waite and Beetham[113] in their study of 2,002 diabetic individuals and 457 non-diabetic persons They noted that in the examination of the cornea with the slit lamp and corneal microscope wrinkles involving Descemet's membrane occurred in 26 per cent of diabetics and in only 10 5 per cent in non-diabetics

Cataracts—It is a common impression and one which is supported by statements in many textbooks that cataracts are more common in diabetics and that there is a characteristic type of cataract seen in diabetes However, this belief was not borne out by the findings of Waite and Beetham in their extensive study They found the incidence of senile and complicated cataracts to be no greater in diabetic than in non-diabetic persons It is true however, that Waite and Beetham found slowly progressive bilateral cataracts in 11 of 297 juvenile diabetics This special type of cataract is characterized by flocculi and fine iridescent crystals in the cortical layer of the lens with later on changes in the posterior cortex at the pole

If patients are properly studied and prepared prior to operation cataract extraction can be carried out in diabetics with no higher incidence of hemorrhage or other complications than in non diabetics Preparation for operation includes careful control of the diabetic condition control of hypertension in so far as possible and correction of any abnormal tendency to bleed As regards the last-named point therapy may include vitamin C supplements rutin and such other medication as may be indicated on the basis of special studies

Retinitis—The ocular complication most feared is that of retinitis That this manifestation of generalized vascular disease is due to the disturbed metabolism of inadequately controlled diabetes seems reasonably certain It has long been recognized that diabetic patients in general are susceptible to retinitis but with middle aged or elderly persons it has been difficult to be sure how much of the disorder was

fants This incidence of success was not much better than that achieved in the pre insulin era from 1898 192 when among 107 pregnancies only 57 or 53 per cent resulted in living births

The abnormalities which characterize pregnancy in the diabetic have been summarized by White[115] as follows

(1) *Maternal* including generalized vascular disease and hypo-ovarianism The incidence of vascular disease in young diabetics has been commented upon repeatedly in this discussion It has been found that if calcification of the pelvic vessels is demonstrable by x ray the chances of securing a living baby are poor (about 1 in 5) Hypofunc tioning of the ovaries is reflected in the amenorrhea and dwarfism seen in young diabetics associated with an increase in the level of follicle stimulating hormone in the blood serum and a low excretion of 17 ketosteroids in the urine Examination of the ovaries often shows atrophy with poor follicle development

(2) *Obstetrical*—*A normal obstetrical course is unusual* The uterus usually is irritable and contractions may be present from the early part of pregnancy In White s series 25 per cent of pregnancies terminated in early spontaneous abortion and in 40 per cent pre-eclampsia occurred Breech presentation was present in 33 per cent and uterine inertia and shoulder dystocia were common

(3) *Chemical*—The lowered renal threshold for sugar which characterizes pregnancy in general may render difficult the treatment of diabetes The renal threshold may be so low that large amounts of sugar may appear in the urine in the presence of satisfactory or normal blood values so that the adjustment of insulin dosage may present a problem A second chemical abnormality is that of disturbance of water balance as manifested by exce sive gain in weight of the mother fol lowed by edema hydramnios and edema of the fetus The third change the importance of which has been emphasized by White is that of the imbalance of sex hormones observed by her in 75 per cent of cases The changes include a fall in the excretion of sodium pregnandiol in the urine a fall in serum estrin and a compensatory rise of serum chorionic gonadotropin (prolan)

(4) *Fetal*—The infants of diabetic mothers are large exceeding normal weight for the period of gestation in 80 per cent of cases The excess weight of the fetus is due both to overnutrition and edema Splanchnomegaly is common Congenital defects usually slight and of minor importance occur in ⅛ of infants Jaundice without hemorrhage or anemia occurs almost routinely Atelectasis of varying degree is

he was unable to conclude with certainty that rutin had been of benefit Some have held in the past that retinal hemorrhages might be due to insulin or to hypoglycemia caused by insulin There is no good evidence to support such a view, and retinitis would appear to be due to the lack of insulin rather than to its use In the prevention of retinitis in the diabetic the only reasonable course is careful continuous control of the disease

Unfortunately retinitis in the diabetic may be extensive and lead to retinitis proliferans and total or partial blindness Apparently the new formation of blood vessels is an attempt on the part of Nature to clear away foreign material such as blood and exudate by the development of collateral circulation The contraction of scar tissue in the vitreous sac may cause separation of the retina Among 110 patients with retinitis proliferans the onset of this complication occurred in 3 patients in the second decade of life and in 30 patients before the age of 30 years[8] However in the series 57 cases or 51 8 per cent developed retinitis proliferans after the age of 50 years In 93 of the 110 cases the duration of diabetes was more than 5 years and in 53 cases more than 15 years prior to the onset of retinitis proliferans Retinitis proliferans almost invariably is accompanied by evidences of generalized vascular disease This is brought out by the fact that among 37 patients dying with retinitis proliferans the cause of death in 14 cases was arteriosclerotic nephritis, in 15 cases cerebral and/or coronary sclerosis in 1 case gangrene and 3 cases uremia Of the 29 patients in which death was due either to arteriosclerotic nephritis or cerebral and coronary arteriosclerosis, 10 were under the age of 35 years at the time of death

Pregnancy in Diabetes

Prior to the discovery of insulin pregnancy in the diabetic was not a great problem since few diabetic women conceived, and the life expectancy of the young woman with diabetes of appreciable severity was not great With the advent of insulin increased length of life became possible and pregnancy no longer carried an appreciable risk to the mother whose diabetes was well regulated However, the chances of securing a living baby remained much less than was true with mothers without diabetes Thus at the George F Baker Clinic between 1922-1936 only 60 per cent of 161 pregnancies resulted in viable in

of the insulin in the morning before breakfast either using the NPH insulin alone or in combination with crystalline insulin mixed in the syringe

In the obstetrical care of the patient various matters are of importance Premature delivery should be the rule in order to forestall late intrauterine death The time selected is usually the latter part of the thirty seventh or the first part of the thirty eighth week In two thirds of White s patients delivery was by Cesarean section This method of delivery was chosen because of the high incidence of uterine inertia shoulder dystocia and breech presentation and the desire to protect a potentially abnormal infant However Cesarean section must not be done routinely and in this as in other aspects of the care of the diabetic individualization should be the rule Cesarean section is carried out

TABLE XX

DAILY INTRAMUSCULARLY DOSES OF PROGESTERONE (PROLUTON) AND ESTROGEN (STILBOESTROL) RECOMMENDED BY WHITE

Week of Pregnancy	*Dosage of Each (mgm)*
6 9	5 25
0 3	10 50
24 27	15 75
28 31	5 00
32 38	50 1 5

Dosage is based on severity of diabetes age at onset and duration of diabetes severity of vascular lesions and previous obstetrical history

under spinal anesthesia with no preliminary sedation If delivery is accomplished by the normal route the amount of sedation should be kept to a minimum When the third stage is carried out under spinal or gas oxygen anesthesia fluids and glucose are administered parenterally both before and after delivery

It is in matters of medication and hormonal therapy that the management of pregnancy in the diabetic differs most from that in the non diabetic In order to keep edema to a minimum the diet should be as low in sodium as possible and ammonium chloride in dosage of 4 to 8 grams a day may be given intermittently A high protein diet has already been mentioned Estrin and progesterone are given in large dosage by White in an attempt to correct the hormonal imbalance characteristic of

common the incidence and extent depending upon the degree of prematurity The blood sugar of the infant at birth is slightly elevated but falls in about 4 hours to a relatively low level and rises in about 8 hours to the level which is average for a newborn infant, 40 to 60 mgm per 100 c c Postmortem findings in infants who have died have included evidence of excessive hematopoiesis in the liver and spleen hyperplasia of pancreatic islet tissue and advanced bone and gonad development

(5) *Placental*—The placenta in diabetic pregnancies is apt to be overly large although occasionally a small one occurs

In attempting to analyze the cause and mechanism of production of the abnormalities just enumerated White takes as a starting point the characteristic of hypo-ovarianism which may be primary and of endocrine origin or secondary to vascular disease She suggests that the placenta in its attempts to compensate for this ovarian deficiency matures rapidly and ages just as rapidly so that the mother s hormonal chemistry at mid term is more nearly that which is normal at term The increase in serum chorionic gonadotropin may be responsible for the advanced bone and gonad development and the excessive hematopoiesis seen so commonly in the infant

Treatment—It is obvious from statements made thus far that the management of pregnancy in the diabetic woman must include more than careful control of diabetes and the furnishing of a diet adequate in all respects Parenthetically it may be well to state that the entire discussion is concerned not with the older woman with mild diabetes or with the woman who has had one or more children and then develops diabetes perhaps in her late twenties or thirties but with the young woman with onset of diabetes under the age of 20 and usually under the age of 15 who after several years of diabetes, becomes pregnant The situation in the two groups is radically different for, whereas the former group poses few problems management of the latter group is most difficult

In the management of the diabetic condition the diet should contain daily from 180 to 225 grams of carbohydrate from 1 to 2 grams of protein per kilogram of body weight and sufficient fat to allow approximately 30 calories per kilogram Suitable doses of NPH or protamine zinc insulin and regular or crystalline insulin should be given before breakfast with regular or crystalline insulin before the noon and evening meals The amount of insulin must be gauged in large part by the determination of the blood sugar at intervals rather than by tests for sugar in the urine If NPH insulin is used it may be possible to give all

The Future of the Diabetic

Now that more than a quarter century has elapsed since insulin became available it is possible and profitable to take account of stock and attempt to evaluate the future of the diabetic In the foregoing pages progress over the last 25 years has been followed in detail and it has been shown how the life of the diabetic has been greatly prolonged and his capacity for useful work made to approach that of the person without diabetes At present the life expectancy for the middle aged diabetic is fully ⅔ to ¾ that of the non diabetic and the individual with onset of diabetes in childhood is for the first time in history living 20 25 and more years after the beginning of the disease It has been shown that with close supervision pregnancies in young diabetics may be carried to successful termination enabling these young women to lead a normal family life Diabetics throughout the world are engaging in almost every occupation and in almost all lines of endeavor open to anyone and with the possible exception of a few occupations such as that of airplane pilots locomotive engineers and others in whose hands the safety of many depends, there is nothing which they cannot do It is no secret that diabetics are to be found in high government posts and as the heads of large business organizations Outstanding scientists are counted among their number Participants and even world champions in certain strenuous and competitive sports include severe diabetics

Despite the above record of achievement much remains to be accomplished for the welfare of diabetics Although with insulin coma can be prevented or successfully treated and so no longer forms an important cause of death with the passage of time it has become evident that with our present inadequate achievement of control after 10 15 or 20 years of diabetes distressing complications intervene These are by and large of a vascular nature and chiefly arteriosclerotic in type affecting the brain extremities heart and kidneys Today fully ⅔ of diabetics succumb to arteriosclerosis and often prematurely Those with onset in childhood may live into the thirties or forties only to die of manifestations of arteriosclerosis and in this age group exitus usually takes place because of chronic nephritis In the last years of such patients manifestations of generalized vascular involvement are evident and the patient dying in uremia may show also sclerosis of arteries throughout the body with coronary heart disease hypertension and retinitis with at times retinitis proliferans and near or total blindness

There is at the present time much discussion as to whether these

diabetic pregnancies There are various possibilities in this connection as regards type of preparation mode of administration and duration of treatment At present White recommends the schedule shown in Table XX

The amounts of stilboestrol indicated are designed to maintain the level of chorionic gonadotropin below 200 rat units per 100 c c of serum between the twenty-fourth and thirty-sixth week of pregnancy The amount of progesterone is gauged to maintain the pregnandiol excretion to as high as the lower limit of normal In addition vitamin supplements are given routinely

Following the above plan of treatment White[5] reported the following results among 352 pregnancies in 330 mothers (only those pregnancies continuing from the 24th week on are included)

Sex hormone balance	Cases no	Fetal survival per cent
Normal	72	97
Abnormal not corrected	62	44
Abnormal corrected by treatment	218	90

There was only one maternal death

The main problem in the post natal care of the infant is that of atelectasis To overcome this the air passages are drained by posture and the stomach drained by posture and by suction which is repeated at intervals during the first hours of life (Gellis, White and Pfeffer[1]) It is a clinical impression that the infant of the diabetic woman has more amniotic fluid in the air passages than that of the normal woman The infant should be placed in an oxygen incubator bed immediately after birth and stimulated to cry at frequent intervals If breathing is sluggish the use of a resuscitator may be helpful Dehydration is brought about by omitting fluids for 3 to 5 days The administration of glucose has not been found necessary

A question which may arise is the desirability for therapeutic abortion and sterilization in the diabetic Only rarely is this justifiable However, in those patients with diabetes of over 20 years duration and particularly in the presence of well marked nephritis retinitis proliferans or calcification of the pelvic blood vessels abortion and sterilization may well be indicated[116] Each case should be considered individually

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Despite the above record of achievement, much remains to be accomplished for the welfare of diabetics. Although with insulin coma can be prevented or successfully treated and so no longer forms an important cause of death, with the passage of time it has become evident that with our present inadequate achievement of control, after 10, 15 or 20 years of diabetes distressing complications intervene. These are by and large of a vascular nature and chiefly arteriosclerotic in type, affecting the brain, extremities, heart and kidneys. Today fully ⅔ of diabetics succumb to arteriosclerosis and often prematurely. Those with onset in childhood may live into the thirties or forties only to die of manifestations of arteriosclerosis, and in this age group exitus usually takes place because of chronic nephritis. In the last years of such patients manifestations of generalized vascular involvement are evident, and the patient dying in uremia may show also sclerosis of arteries throughout the body with coronary heart disease, hypertension and retinitis, with at times retinitis proliferans and near or total blindness.

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late degenerative complications are due to inadequate control of the diabetic condition or whether they are related simply to some unknown factor plus the duration of the diabetic condition The writer and his associates for reasons already given, have taken the stand that the late as well as the acute complications are due to inadequately controlled diabetes They are so noticeable in young people because of the admitted difficulty of maintaining physiological conditions in such patients over 20 to 25 years of time They are probably just as operative as in those persons with onset of diabetes in middle life and beyond but not so noticeable to the casual observer because after 20 years of diabetes these persons have arrived at an age at which death often takes place in persons in the general population anyway and at which arteriosclerosis for causes other than diabetic is frequent

By educational measures directed at the patient and his family the general public and the medical profession great strides have already been taken in reducing the morbidity and mortality from the acute complications of diabetes Some progress has been made toward postponement and better treatment of the late complications What then does the future hold for the diabetic Along what lines should the greatest endeavor be made? The writer believes that these may be summarized as follows

(1) Earlier and more complete recognition of diabetes throughout the general population so that the hidden diabetics which probably number as many as those already recognized may be brought to light One does not prevent diabetes in this way, but one can hope to prevent progression of the disease and prevent or defer complications

(2) Better understanding of the pathological physiology of diabetes Despite the great amount of work which has been done in recent years the basic defect in diabetes is not known and the influences which precipitate diabetes in the predisposed are still in the stage of speculation The benefits of insulin are grossly known and visible to all but very little indeed is known as to the exact action and site of insulin although much recent work has helped in this regard As yet very little in a concrete way is understood as to the mechanism whereby diabetes favors premature arteriosclerosis and other types of blood vessel damage Even partial solution of this major problem would benefit not only the diabetic but possibly also the non-diabetic who also in later years is highly susceptible to vascular disease

(3) Energetic treatment of diabetes from the moment of diagnosis of the disease keeping in mind the ideal of establishing physiological

conditions in so far as practicable It is realized that perhaps more often than not a compromise will have to be made between what is the ideal and what is practical but unless the goal is set at 100 per cent control one has very little chance of achieving anywhere near that Unrestricted diets disregard of hyperglycemia and glycosuria and other free and easy forms of treatment are to be condemned

(4) Development of newer and better types of insulin which will make possible day after day more continuous control of diabetes throughout the entire 24 hours If insulin could be synthesized and the present laborious method of extraction be discarded a major victory would have been won One may even bear in mind that the prevention or cure of diabetes may not be impossible although admittedly no progress has been made to date along this line except with experimental animals

The outlook of the diabetic cannot be foreseen with any certainty but with the wealth of information and experience now available one can look forward confidently to a future in which an even happier longer and more useful life will be possible

BIBLIOGRAPHY

1 JOSLIN E P and LOMBARD H L *Diabetes epidemiology from death records* New Eng Jour Med 1936 CCXIV 7

2 LOMBARD H L and JOSLIN E P Certification of death of 1 000 diabetic patients Am Jour Digest Dis 1947 XIV 275

3 PALMER L J Cited by Joslin and Lombard[1]

4 MARKS H H Recent statistics on diabetes and diabetics Med Clin North Am 1947 XXXI 369

5 U S PUBLIC HEALTH SERVICE Magnitude of chronic disease problem in the United States National Health Survey 1935 36 Sickness and Medical Care Series Bulletin No 6 1938

6 BLOTNER H Studies in glycosuria and diabetes mellitus in selectees Jour Am Med Assoc 1946 CXXXI 1109

7 WILKERSON H L C and KRALL L P Diabetes in a New England town A study of 3 516 persons in Oxford Mass Jour Am Med Assoc 1947 CXXXV 209

8 JOSLIN E P ROOT H F WHITE P MARBLE A and BAILEY C C The Treatment of Diabetes Mellitus 8th Ed Lea and Febiger Philadelphia 1946

9 PINCUS, G and WHITE P On the inheritance of diabetes mellitus I An analysis of 675 family histories Am Jour Med Sci 1933 CLXXXVI 1 II Further analysis of family histories Ibid 1934, CLXXXVIII 159 III The blood sugar values of the relatives of diabetics Ibid 1934 CLXXXVIII 787

10 SPRAGUE, R G Diabetes mellitus associated with chronic relapsing pancreatitis Proc Staff Meet Mayo Clinic 1947 XXII 553

11 JOSLIN, E P The relation of trauma to diabetes, Ann Surg, 1943 CXVII, 607

12 SOSKIN S Liver and carbohydrate metabolism Endocrinology 1940 XXVI, 297

13 SOSKIN S and LEVINE R Carbohydrate Metabolism University of Chicago Press Chicago 1946

14 WEINHOUSE S MEDES G and FLOYD N F Fatty acid metabolism The mechanism of ketone body synthesis from fatty acids with isotopic carbon as tracer Jour Biol Chem 1944, CLV 143

15 BEST, C H and TAYLOR N B The Physiological Basis of Medical Practice 4th Edition p 571 Williams and Wilkins Co Baltimore 1945

16 CORI C F Enzymatic reactions in carbohydrate metabolism Harvey Lectures 1945-46 XLI 253

17 STETTEN D, JR The endocrine regulation of carbohydrate metabolism Jour Am Med Assoc 1946 CXXXII 373

18 STETTEN D JR and BOXER G E Studies in carbohydrate metabolism Rate of turnover of liver and carcass glycogen studied with aid of deuterium Jour Biol Chem 1944 CLV 231

19 HOUSSAY B A Carbohydrate metabolism New Eng Jour Med 1936 CCXIV 971

20 EVANS H M MEYER K SIMPSON M E and REICHERT F I Disturbance of carbohydrate metabolism in normal dogs injected with hypophyseal growth hormone Proceed Soc Exper Biol and Med 1932 XXIX 857

21 YOUNG F G Permanent experimental diabetes produced by pituitary (anterior lobe) injections Lancet 1937, II 372

22 LUKENS F D W DOHAN F C and WOLCOTT M W Pituitary diabetes in cat recovery following phlorhizin treatment Endocrinology 1943 XXXII 475

23 LONG C N H Influence of pituitary and adrenal glands upon pancreatic diabetes Harvey Lectures 1936-37 XXXII 194

4 INGLE, D J SHEPPARD R EVANS J S and KUIZENGA M H Comparison of adrenal steroid diabetes and pancreatic diabetes in rat Endocrinology 1945 XXXVII 341

25 HOUSSAY B A Thyroid and metathyroid diabetes Endocrinology 1944 XXXV 158

26 McHENRY E W and PATTERSON J M Lipotropic factors Physiol Reviews 1944 XXIV 1 8

27 WHITE P MARBLE, A BOGAN I K and SMITH R M Enlargement of the liver in diabetic children II The effect of raw pancreas betaine hydrochloride and protamine insulin Arch Int Med 1938 LXII 751

8 DRAGSTEDT, L R PROHASKA J V and HARMS H P Observations on a substance (a fat metabolizing hormone) which permits survival and prevents liver changes in depancreatized dogs Am Jour Physiol 1936 CXVII 175

9 WIENER H Über Zersetzung und Bildung der Harnsaure im Thierkorper Arch f exper Path u Pharm 1899 XLII 375

30 JACOBS H R Hypoglycemic action of alloxan Proceed Soc Exper Biol and Med 1937 XXXVII 407

31 DUNN J S SHEEHAN H L and McLETCHIE N G B Necrosis of islets of Langerhans produced experimentally Lancet 1943 I 484

32 BAILEY C C and BAILEY O T The production of diabetes mellitus in rabbits with alloxan Jour Am Med Assoc 1943 CXXII 1165

33 GOLDNER M G GOMORI G BRUNSCHWIG A and ALLEN J G Alloxan Jour Am Med Assoc 1943 CXXII 966

34 GRIFFITHS M Uric acid diabetes Jour Biol Chem 1948 CLXXII 853

35 CONN J W LOUIS L H and WHEELER C E Production of temporary diabetes mellitus in man with pituitary adrenocorticotropic hormone relation to uric acid metabolism Jour Lab and Clin Med 1948 XXXIII 651

36 TALBOT N B CRAWFORD J D and BAILEY C C Use of mesoxalyl urea (alloxan) in treatment of an infant with convulsions due to idiopathic hypoglycemia Pediatrics 1948 I 337

37 BAILEY C C and LeCOMPTE P Clinical implications of alloxan diabetes Med Clin N America 1947 XXXI 4 7

38 LUKENS F D W Alloxan diabetes Physiol Reviews 1948 XXVIII 304

39 DOHAN F C and LUKENS, F D W Lesions of the pancreatic islets produced in cats by administration of glucose Science, 1947 CV 183
40 LAGUESSE M E Sur la formation des ilots de Langerhans dans le pancreas Compt rend Soc de Biol 1893 XLV, 819
41 ZUELZER G Experimentelle Untersuchungen uber der Diabetes Berlin Klin Wochnschr 1907 XLIV, 474
42 BANTING F G and BEST C H The internal section of the pancreas Jour Lab and Clin Med 1921 VII -51
43 JENSEN H Insulin Its Chemistry and Physiology The Common wealth Fund New York 1939
44 SCOTT D A and FISHER A M Insulin and zinc content of normal and diabetic pancreas Jour Clin Invest 1938, XVII 7 5
45 HAIST R E CAMPBELL J and BEST C H The prevention of diabetes New Eng Jour Med, 1940 CCXXIII, 607
46 WAUGH J M DIXON C F CLAGETT O T BOLLMAN J L SPRAGUE R G and COMFORT M Total pancreatectomy A symposium presenting four successful cases and a report on metabolic observations Proceed Staff Meet Mayo Clinic 1946 XXI 25
47 DRIVER R L and MURLIN, J R Further studies on aids to the absorption of insulin from the G I tract Am Jour Physiol 1939, CXXVI P480
48 GLASS W L SPINGARN C L and POLLACK H Unusually high insulin requirements of diabetes mellitus Arch Int Med 194 LXX 221
49 MARBLE A Insulin resistance Report of a case of marked in sensitiveness of long duration without demonstrable cause Arch Int Med 1938 LXII 432
50 FALTA W Renaler and Insularer Diabetes page 7 Urban and Schwarzenberg Berlin and Vienna 1939
51 HIMSWORTH H P Diabetes mellitus Its differentiation into in sulin-sensitive and insulin insensitive types Lancet 1936 I 1 7
5- WARREN S The Pathology of Diabetes Mellitus 2nd Ed Lea and Febiger Philadelphia 1938
53 KIMMELSTIEL P and WILSON, C Intercapillary lesions in the glomeruli of the kidney Am Jour Path 1936, XII 83
54 KIMMELSTIEL P and PORTER W B Intercapillary glomerulosclerosis New Eng Jour Med 1948 CCXXXVIII 876 and 909
55 JOSLIN E P and ASSOCIATES Diabetes mellitus Postgraduate Med, 1949 V 139

56 METROPOLITAN LIFE INSURANCE CO Statistical Bulletin 1947 XXVIII 7
57 EXTON W G and ROSE A R One hour two dose dextrose tolerance test Am Jour Clin Path 1934 IV 381
58 SMITH M A micro modification of the method of Benedict for the quantitative determination of reducing sugar in urine Jour Lab and Clin Med 19 VII 364
59 EXTON W G Diabetes and Bright s disease as selection problems Proceedings of the Twenty eighth Annual Meeting Medical Section American Life Convention June 1939
60 NELSON N A photometric adaptation of the Somogyi method for the determination of glucose Jour Biol Chem 1944 CLIII 375
61 MARBLE A and VARTIAINEN I Crystalline insulin Jour Am Med Assoc 1939 CXIII 1303
62 HAGEDORN H C JENSEN B N KRARUP N B and WODSTRUP I Protamine insulinate Jour Am Med Assoc 1936 CVI 177
63 SCOTT D A and FISHER A M Studies on insulin with protamine Jour Pharm and Exper Therap 1936 LVIII 78
64 REINER L SEARLE D S and LANG E H Insulin preparations with prolonged activity I Globin insulin Proceed Soc Exper Biol and Med 1939 XL 170
65 BAILEY C C and MARBLE, A Histone zinc insulin globin (zinc) insulin and clear protamine zinc insulin A comparative study of their action Jour Am Med Assoc 194 CXVIII 683
66 MACBRYDE C M and REISS R S Modified protamine zinc insulin Comparison with globin zinc insulin and insulin mixtures Jour Clin Endocrinol 1944 IV 469
67 PECK F B Insulin mixtures and modifications Med Clin N America 1947 XXXI 343
68 COLWELL A R Effective insulin timing in diabetes mellitus Med Clin N America 1947 XXXI 3 7
69 NEWBURGH L H and CONN J W New interpretation of hyperglycemia in obese middle aged persons Jour Am Med Assoc 1939 CXII 7
70 MARBLE, A and SMITH R M Atrophy of subcutaneous fat following injections of insulin Proceed Am Diabetes Assoc 194 II 171
71 OESTREICHER D L Insulin fat atrophy in diabetes mellitus Thesis Univ of Western Ontario Canada 1947
7 MARBLE A and SMITH R M Exercise in diabetes mellitus Arch Int Med 1936 LVIII 577

73 MARBLE A WHITE P BOGAN, I K and SMITH R M Enlargement of the liver in diabetic children I Incidence etiology and nature of the hepatomegaly Arch Int Med, 1938, LXII 740
74 WHITE P Arteriosclerosis in juvenile diabetes paper read at a seminar of the Metabolism and Endocrinology Study Section Division of Research Grants and Fellowships U S Public Health Service at the Beckman Hotel New York N Y, October 5 1947
75 HOLLER J W Potassium deficiency occurring during treatment of diabetic acidosis Jour Am Med Assoc 1946 CXXXI 1186
76 GUEST G M Organic phosphates of the blood and mineral metabolism in diabetic acidosis Am Jour Dis Child 1942 LXIV 401
77 MARBLE A Hypoglcemia due to insulin New Eng Jour Med., 1937, CCXVII 130
78 ROOT H F The use of insulin and the abuse of glucose in the treatment of diabetic coma Jour Amer Med Assoc, 1945 CXXVII 557 see also ROOT H F The use of glucose in the treatment of diabetic coma Jour Clin Endocrin 1945 V 353
79 ROOT, H F Anuria following diabetic coma relieved by hypertonic salt solution Jour Am Med Assoc 1934 CIII 48 see also ROOT H F Intravenous administration of hypertonic salt solution for anuria in patients with one kidney Ibid 1937 CVIII 947
80 COLLENS W S and WILENSKY N D Intermittent venous occlusion in treatment of peripheral vascular disease experience with 1 4 cases Jour Am Med Assoc 1937 CIX -1 5
81 KATZ R A A preliminary report on a medical treatment of diabetic ischemic gangrene with diethyl ether, Proceed Am Diabetes Assoc 1946 VI 471
82 WIRTSCHAFTER Z T and WIDMANN R The elaboration of histamine in vivo in the treatment of peripheral vascular disorders A preliminary report Jour Am Med Assoc, 1947 CXXXIII 604
83 McKITTRICK L S Recent advances in the care of surgical complications of diabetes mellitus New Eng Jour Med 1946 CCXXXV 9 9
84 ROOT H F Factors favoring successful transmetatarsal amputation in diabetes New Eng Jour Med 1948 CCXXXIX 453
85 CROSSMAN L W RUGGIERO W F HURLEY V and ALLEN F M Reduced temperatures in surgery II Amputation for peripheral vascular disease Arch Surg 194 XLIV 139
86 ROOT H F BLAND E F GORDON W H and WHITE P D Coronary atherosclerosis in diabetes mellitus Jour Am Med Assoc 1939 CXIII -7

87 MILLARD E B and ROOT H F Degenerative vascular lesions and diabetes mellitus Am Jour Digest Dis 1948 XV 41
88 MANN G V CARDNI R C and ROOT H F Renal complications of diabetes mellitus Bull New Eng Med Center 1948 X 170
89 ROBBINS S L and TUCKER A W The cause of death in diabetes New Eng Jour Med 1944 CCXXXI 865
90 JORDAN W R Neuritic manifestations in diabetes mellitus Arch Int Med 1936 LVII 307
91 RUNDLES R W Diabetic neuropathy General review with report of 1 5 cases Medicine 1945 XXIV 111
9 TREUSCH J V Diabetic neuritis A tentative working classification Proceed Staff Meet Mayo Clinic 1945 XX 393
93 BAILEY C C and ROOT H F Neuropathic foot lesions in diabetes mellitus New Eng Jour Med 1947 CCXXXVI 397
94 SHERIDAN E P and BAILEY C C Diabetic nocturnal diarrhea Jour Am Med Assoc 1946 CXXX 63
95 HILDEBRAND A G MONTGOMERY H and RYNEARSON E H Necrobiosis lipoidica diabeticorum Arch Int Med 1940 LXVI 851
96 KENT H A See reference 8
97 WILDER R M Clinical Diabetes Mellitus and Hyperinsulinism W B Saunders Co Philadelphia 1940
98 JORDAN W R See reference 8
99 SHELDON J H Haemochromatosis Oxford Univ Press London 1935
100 RATH C E and FINCH C A Chemical clinical and immunological studies on the products of human plasma fractionation XXXVIII Serum iron transport Measurement of iron binding capacity of serum in man Jour Clin Invest 1949 XXVIII 79
101 ROUS P Urinary siderosis Hemosiderin granules in the urine as an aid in the diagnosis of pernicious anemia hemochromatosis and other diseases causing siderosis of the kidney Jour Exper Med 1918 XXVIII 645
10 FISHBACK H R Clinical demonstration of iron in skin in hemochromatosis Jour Lab and Clin Med., 1939 XXV 98
103 DAVIDOFF L M and CUSHING H Studies in acromegaly disturbances of carbohydrate metabolism, Arch Int Med 19 7 XXXIX 751
104 COGGESHALL, C. and ROOT H F Acromegaly and diabetes mellitus Endocrinology 1940 XXVI, 1

105 WILDER R M FOSTER R F and PEMBERTON J de J Total thyroidectomy in diabetes mellitus Endocrinology 1934 XVIII 455
106 RUDY A BLUMGART H L and BERLIN D D Carbohydrate metabolism in human hypothyroidism induced by total thyroidectomy III A case of diabetes mellitus treated by total ablation of the normal thyroid gland Am Jour Med Sci 1935, CXC 51
107 SHEPARDSON H C and WEVER G K Myxedema and diabetes mellitus with report of case, Internat Clin 1934 IV, 133
108 DUNCAN L E Jr SEMANS J H and HOWARD J E Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus disappearance of diabetes after removal of the tumor Ann Int Med 1944 XX 815
109 GREEN D M Pheochromocytoma Jour Am Med Assoc 1946 CXXXI 1260
110 MARKS J H and HAM D P Calcification of the vas deferens Am Jour Roent and Radium Therapy 1942 XLVII 859
111 STEARNS S FRIEDMAN E LUGIECH M and HOFFMAN S H Lipemia retinalis Report of a case, New Eng Jour Med 1948 CCXXXVIII 16
112 MARBLE A and SMITH R M Blood lipids in lipaemia retinalis Arch Ophth 1936 XV 86
113 WAITE J H and BEETHAM W P The visual mechanism in diabetes mellitus a comparative study of 2002 diabetics and 457 non diabetics for control New Eng Jour Med, 1935 CCXII 367 and 429
114 RODRIGUEZ R and ROOT, H F Capillary fragility and diabetic retinitis with a note on the use of rutin New Eng Jour Med 1948 CCXXXVIII 391
115 WHITE, P Pregnancy complicating diabetes Proceed Am Diabetes Assoc 1946 VI 259
116 WHITE P Pregnancy complicating diabetes of more than twenty years duration Med Clin North Am 1947, XXXI 395 see also WHITE P Pregnancy complicating diabetes Am Jour Med 1949 VII 609
117 COLLINS WILLIAMS J and BAILEY C C Effect of uric acid in glutathione deficient rabbits Proceed Soc Exper Biol and Med 1949 LXXI 583
118 SMELO L S Insulin resistance Proceed Am Diabetic Assoc 1948 VIII 75
119 GOFMAN J W and ASSOCIATES Blood lipids and human atherosclerosis Circulation 1950 II 161

1 0 COLLENS W S BOAS L C ZILINSKY J D and GREENWALD J J Lipoatrophy following the injection of insulin a method of control New Eng Jour Med 1949 CCXLI 610

1 1 RENOLD A E MARBLE A and FAWCETT D W Action of insulin on deposition of glycogen and storage of fat in adipose tissue Endocrinology 1950 XLVI 55

12 MARBLE A and RENOLD A E Atrophy and hypertrophy of fat due to insulin Transact Assoc Am Phys 1949 LXII 19

123 NADLER C S BELLET S DILLON E S and LANNING M Studies on the serum potassium in diabetic acidosis Proceed Am Diabetic Assoc 1949 IX 63

1 4 PRATT T C The diabetic as a surgical risk Bull New York Acad Med 1950 XXVI 786

1 5 JOSLIN E P and WILSON J L Lessons for future treatment from 472 fatalities in diabetic children Brit Med Jour 1950 II 1293

1 6 BARNES R H Capillary fragility studies in diabetes mellitus and the use of rutin in diabetic retinitis Am Jour Med Sci 1950 CCXIX 368

1 7 GELLIS S S WHITE P and PFEFFER W Gastric suction a proposed additional technic for the prevention of asphyxia in infants delivered by Cesarean section a preliminary report New Eng Jour Med 1949 CCXL 533

1 8 BUTLER A M Medical progress diabetic coma New Eng Jour Med 1950 CCXLIII 648

1 9 GABRIELL A J and MARPLE A Clinical experience with a new modified protein insulin NPH , Am Jour Digest Dis 1949 XVI 197

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105 WILDER R M FOSTER R F and PEMBERTON J de J Total thyroidectomy in diabetes mellitus Endocrinology 1934, XVIII 455
106 RUDY A BLUMGART H L and BERLIN, D D Carbohydrate metabolism in human hypothyroidism induced by total thyroidectomy III A case of diabetes mellitus treated by total ablation of the normal thyroid gland Am Jour Med Sci 1935 CXC 51
107 SHEPARDSON H C and WEVER G K Myxedema and diabetes mellitus with report of case, Internat Clin 1934 IV 133
108 DUNCAN L E Jr SEMANS J H and HOWARD J E Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus disappearance of diabetes after removal of the tumor Ann Int Med 1944 XX 815
109 GREEN D M Pheochromocytoma Jour Am Med Assoc 1946 CXXXI, 1260
110 MARKS J H and HAM D P Calcification of the vas deferens Am Jour Roent and Radium Therapy, 194 XLVII 859
111 STEARNS S FRIEDMAN E LUGITCH M and HOFFMAN S H Lipemia retinalis Report of a case New Eng Jour Med 1948 CCXXXVIII 16
112 MARBLE A and SMITH R M Blood lipids in lipaemia retinalis Arch Ophth 1936 XV 86
113 WAITE J H and BEETHAM W P The visual mechanism in diabetes mellitus a comparative study of 2002 diabetics and 457 non diabetics for control New Eng Jour Med 1935 CCXII 367 and 4 9
114 RODRIGUEZ R and ROOT H F Capillary fragility and diabetic retinitis with a note on the use of rutin New Eng Jour Med 1948 CCXXXVIII 391
115 WHITE P Pregnancy complicating diabetes Proceed Am Diabetes Assoc 1946 VI 259
116 WHITE P Pregnancy complicating diabetes of more than twenty years duration Med Clin North Am 1947 XXXI 395 see also WHITE P Pregnancy complicating diabetes Am Jour Med. 1949 VII 609
117 COLLINS WILLIAMS J and BAILEY C C Effect of uric acid in glutathione deficient rabbits Proceed Soc Exper Biol and Med 1949 LXXI 583
118 SMELO L S Insulin resistance Proceed Am Diabetic Assoc 1948 VIII 75
119 GOFMAN J W and ASSOCIATES Blood lipids and human atherosclerosis Circulation 1950 II 161

CHAPTER V-A

NONDIABETIC MELITURIA

INCLUDING RENAL GLYCOSURIA

By ALEXANDER MARBLE

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Definition.—Nondiabetic melituria is a term applied to those conditions apart from diabetes mellitus in which sugar appears in the urine. Such melituria may be divided into the following groups: (1) renal glycosuria, (2) unclassified glycosuria, (3) pentosuria, (4) fructosuria, (5) lactosuria and (6) galactosuria. Other types of melituria of less importance are mannoheptulosuria and sucrosuria. In any patient with persistent meliturja of significant degree it is incumbent upon the physician to take immediate steps to establish a definite diagnosis. If diabetes is proved not to be present, then further procedures should be carried out without delay in order to establish the nature of the sugar which is excreted. This information is of value to the patient not only

160 mgm per 100 c c Probably many of the instances of so called alimentary glycosuria fall in this category However since to include all such persons under the head of renal glycosuria would result in the grouping together of a variety of conditions the writer and his associates have restricted the diagnosis of renal glycosuria to those persons who exhibit persistent glycosuria even in the fasting state[3] This is equivalent to stating that the threshold for sugar is as low as 100 mgm per 100 c c or lower If this diagnostic standard is used then the diagnosis of renal glycosuria will be made only infrequently Thus among 2 800 cases of melituria seen at the George F Baker Clinic there were only 76 cases of renal glycosuria (including 9 cases of renal glycosuria of pregnancy) using the term in the limited sense described Among 4 000 cases of glycosuria at the Montreal General Hospital Fowler[4] found only 7 cases with constant glycosuria

In renal glycosuria the blood sugar both before and after food and glucose is within a normal range The amount of sugar excreted in the urine may be small or large and is partly dependent upon diet In those patients in whom accurate studies have been carried out no impairment in the storage and utilization of carbohydrate has been found

It is at times desirable to know the approximate level of the renal threshold A suitable procedure is to withhold food in the morning and to take specimens of urine and arterial (capillary) blood at half hourly intervals If with the passage of time it becomes apparent that the blood sugar will not fall low enough to permit disappearance of glycosuria then a dose of regular or crystalline insulin usually 10 or 12 units may be given and the collection of blood and urine specimens at half hourly intervals continued The level of blood sugar at the time at which the urinary sugar clears up represents the approximate threshold In patients in whom the threshold is not at such low levels but above 100 mgm per 100 c c it is possible to determine it by tests of the urine and capillary blood for sugar at 15 to 30 minute intervals following the giving of 50 to 100 gm of glucose by mouth Because of the lag which often causes an apparent discrepancy between the blood and urine findings the threshold may be estimated by study of both the ascending and descending limbs of the tolerance curve Rarely is catheterization justifiable for the sake of the test alone but more accurate data are possible thereby

Corcoran has described another method by which may be found the approximate level of blood sugar at which glycosuria will begin This

for reassurance that diabetes is not present, but also because it may make it possible for him to pass examinations for life insurance and other purposes without penalization

Various preliminary diagnostic steps including the carrying out of glucose tolerance tests are outlined in detail in the preceding chapter

RENAL GLYCOSURIA

Definition — Renal glycosuria (orthoglycemia glycosuria renal diabetes) is a condition in which the 'renal threshold' for glucose is lower than the average normal of approximately 140 to 180 mgm of sugar per 100 c c of blood (capillary blood, Folin methods) Because of this glucose appears in the urine at levels of blood sugar which may in extreme cases be below 100 mgm per 100 c c It is to be thought of not as a disease but as a deviation from the average normal and is due probably to incomplete reabsorption of sugar from the glomerular filtrate by the renal tubules This in turn is apparently due to an abnormality in the phosphorylation mechanism

It is well to point out that, although the concept of a "renal threshold" for sugar may be useful clinically, it is not exact and may be misleading[1] Actually the appearance of glucose in the urine as it reaches the kidney pelvis depends upon three factors (1) the level of blood glucose, (2) the rate of glomerular filtration and (3) the efficiency with which the filtered glucose is reabsorbed by the tubules The tubules normally can reabsorb glucose up to a certain quantity (about 300 to 350 mgm per minute) but when this capacity is overtaxed as in the presence of an abnormally high level of blood sugar in diabetes glycosuria occurs As an example of the influence of the rate of glomerular filtration one may cite the elevated 'renal threshold' found in certain cases of diabetes with concomitant nephritis and uremia in which because of glomerular damage glycosuria may not occur despite levels of blood sugar of 300 to 400 mgm per 100 c c Finally in renal glycosuria is seen the effect of the third factor, that of impaired efficiency of tubular reabsorption

Diagnosis — The frequency with which renal glycosuria is diagnosed will depend upon the criteria used by the physician concerned It is certain that the "renal threshold" in many individuals is slightly or moderately lower than in the average normal, such persons will excrete sugar in the urine only after a meal when the blood sugar rises to 130 to

a physiological event It is important to determine whether or not the pregnant woman has a benign glycosuria or true diabetes Consequently tests of the blood and urine for sugar should be made at 45 to 60 minutes after a regular meal If such tests are not conclusive then a formal glucose tolerance test should be done Diabetes may have its onset during pregnancy or a diabetic may become pregnant If the studies of the blood sugar during pregnancy do not yield values which are unequivocably normal then following delivery the patient should be seen by the physician every 3 months for the first year and at such visits tests of the blood and urine for sugar should be made 45 to 60 minutes after a regular meal

Prognosis — The question naturally arises as to whether or not renal glycosuria is a permanent condition Data are not complete enough to give a definite answer to the question One knows that the threshold for sugar is temporarily lowered during pregnancy and that following delivery the previous threshold is regained One knows further that with increasing age there is a tendency for increasing elevation of the renal threshold In the presence of renal block and uremia in a diabetic the threshold may be as high as 300 to 400 mgm per 100 c c Consequently it seems possible that the renal threshold for sugar need not remain at a given level throughout life It is fair to state however that in the small group of renal glycosurics studied at the George F Baker Clinic over many years of time the threshold has remained low

Although renal glycosuria does not progress to true diabetes a lowered renal threshold may of course be present in the diabetic as well as in the non diabetic person It seems reasonable to suppose that if one could follow over a period of years a large group of individuals with a low threshold for sugar some of them possessing influences favorable for the development of diabetes such as the presence of diabetes in relatives obesity etc would develop true diabetes However this is true among individuals in the general population and does not necessarily point to any connection between diabetes and renal glycosuria

The most striking case of long standing renal glycosuria known to the writer is that of a man born in 1884 in whom urinary sugar was first discovered at the age of 10 years During the last 56 years sugar has been found in sizable amounts at every examination of the urine and at times in quantities as great as 5 per cent or more He has restricted his diet little if any He has remained in good health and has 5 healthy children

is calculated from the "maximum glucose reabsorptive capacity" of the tubules as determined from the urea clearance and concurrent blood and urine sugar estimations

Clinical Features — Renal glycosuria is a condition set apart from diabetes mellitus and if care is used in making the diagnosis, no progression to diabetes will be found Care must be taken in arriving at a diagnosis in those patients with persistent glycosuria in whom following food or glucose the blood sugar rises somewhat higher than the average normal but not quite to diabetic levels In such patients the physician will do well not to make the diagnosis of renal glycosuria but rather that of *potential diabetes* and place the patient under careful observation for an indefinite period If in a person with persistent glycosuria, the glucose tolerance test reveals a flat curve or one which rises only slightly or moderately and well within normal limits, the chances are overwhelming that the condition is not pre diabetic, and the patient and his family may be given a good prognosis

The patient with renal glycosuria does not have the characteristic symptoms of diabetes It is instructive that despite persistent marked glycosuria there is no polyuria and polydipsia Some patients complain of easy fatiguability and lassitude but due to the non specific character of these symptoms, it is always difficult to decide whether they are due to the renal glycosuria

Renal glycosuria is probably an inherited condition[6] It is not clear just why a relatively high percentage of persons with renal glycosuria also have diabetes in relatives Renal glycosuria is a harmless condition There is no known specific pathology

Treatment — Treatment of renal glycosuria is unnecessary although in patients with an extremely low threshold it seems reasonable to advise restriction of sugar, sweets and pastries to avoid increase of wastage in the urine Otherwise a liberal and varied diet should be urged During the first year after diagnosis the patient should report to his physician every three months and subsequently at least annually At such visits in addition to a general physical examination the urine and blood sugar should be tested for sugar at 45 to 60 minutes after an ordinary meal

Renal Glycosuria of Pregnancy — A lowering of the renal threshold for sugar occurs frequently in pregnant women and is seen 4 times as commonly in the second half as in the first half of pregnancy Sugar in the urine during pregnancy is practically always glucose except during the last days when lactose may appear During lactation lactosuria is

of potential diabetics also that the most careful program of follow up should be carried out

Melituria Other Than Glycosuria

It must be kept in mind that in cases of persistent melituria the sugar excreted in the urine may not be glucose but instead may be pentose fructose lactose galactose or sucrose It is important that these conditions be recognized because they have no relationship to diabetes mellitus and their differentiation from diabetes may be a matter of great importance and satisfaction to the patient

At the outset it must be recognized that occasionally substances in the urine other than sugar may cause a slight reduction in alkaline copper solutions Among these are glycuronic acid conjugated glycuronates creatinine and uric acid in concentrated specimens and chloroform used as a preservative However if the reagent used is Benedict s solution a falsely positive test will not often be encountered and is rarely of clinical importance Leaving these substances aside one may carry out in logical sequence a series of diagnostic steps designed to show the exact nature of the sugar which is being excreted in the urine These steps are as follows

(1) *Benedict s test* now used more widely than any other is positive for all sugars which may be found in the urine except sucrose which very rarely has been reported However keto-sugars such as pentose and fructose reduce copper solutions more rapidly and at a lower temperature than does glucose and advantage may be taken of this fact in the differential diagnosis With urine containing pentose reduction of copper solutions takes place within 10 minutes at 50 to 60 C and after a few hours at room temperature without heat Fructose reduces Benedict s solution quickly at 50 to 60 C but much more slowly than pentose at temperatures below 40 C

In actual practice it is helpful to establish a routine by which the urine of all patients with melituria not proven diabetic is tested for sugar not only by the standard Benedict s test but also by setting up the test and allowing the tube to stand at room temperature overnight If pentose and fructose are present in appreciable amounts reduction of the copper solution will take place at room temperature by morning and this lead in diagnosis may be followed up by more exact tests A quicker and more satisfactory way if proper water bath facilities exist is to place the tube with the urine and Benedict s solution in a bath at

"Unclassified" Glycosuria

In the chapter on "Diabetes Mellitus" the diagnosis of "unclassified glycosuria has already been mentioned as covering that group of patients in whom small amounts of sugar appear transiently in the urine despite blood sugar values which do not rise above accepted upper limits of normal Those patients in the group, whose glycosuria varies with diet and whose blood sugar values are at the upper limit of normal, are best placed in a special category of '*potential diabetes*", so that they may be the subjects of an unusually careful follow-up However leaving these aside, there remains a large group of individuals in whom slight, intermittent glycosuria occurs The cause of the transient glycosuria is not always evident although in many instances it must represent partial failure of the normal mechanism for reabsorption of sugar from the kidney tubules as in phloridzin glycosuria or in conditions of tubular damage (nephrosis or poisoning by certain heavy metals) Perhaps in many instances the renal threshold may be slightly or moderately lower than that of the normal average person and a rise in blood sugar occasioned by sugar, food or natural hormonal influences may be just great enough to exceed this somewhat lowered threshold Following are listed conditions with which nondiabetic glycosuria may be associated, acute infections and toxemias increased activity of the thyroid, pituitary or adrenal glands alimentary glycosuria, brain tumors cerebral hemorrhage or skull injuries presumably causing stimulation of intracranial nerve centers chronic or degenerative conditions involving particularly the liver anesthesia or asphyxia nephritis or nephrosis chemical poisoning as from phloridzin, bichloride of mercury chloroform carbon monoxide caffeine morphine, strychnine, uranium lead and dichromate

Each patient constitutes a special problem and must be studied individually In all cases of persistent glycosuria of significant degree positive efforts should be made at once to establish a diagnosis The first steps should be the determination of the blood sugar and urine sugar at 45 to 60 minutes after a liberal meal and if the results of such studies are inconclusive then resort may be had to a formal glucose tolerance test The latter will be necessary in only a small percentage of patients because usually the diagnosis will be apparent from the results of simpler studies Treatment of unclassified glycosuria is that of the underlying condition Restriction of carbohydrate is not necessary except in the group of potential diabetics in whom moderate restriction of carbohydrate by omission of sweets and pastries is desirable It is in the group

harmless asymptomatic and has no relationship to diabetes mellitus There seems little doubt but that pentosuria is inherited probably as a recessive trait In a study of the origins of pentosuric individuals chiefly in the New York area Lasker[8] found that their forebears came from foci of relatively limited extent chiefly in what was formerly Poland and to a less degree in Germany By the systematic examination of urine specimens of large groups of high school students and by contacts with physicians Lasker has collected data concerning over 100 cases of pentosuria The files of life insurance companies contain an appreciable number of individuals with pentosuria although publication of such data usually is not made In our series there are 9 patients with chronic essential pentosuria All are Jews all but . are males and the ages at the time of first discovery of sugar range from 8 to 31 6 years The 9 patients continue in good health and show no tendency to progression to diabetes despite the fact that melituria in all patients has been known to exist for at least 9 years and in 6 cases for 20 years or more The presence of pentosuria is not regarded by life insurance companies as detracting from an applicant s insurability

Fructosuria — Essential fructorsuria or levulosuria is an even rarer condition than pentosuria Like pentosuria it is probably an inherited condition and consists of a benign metabolic error In such persons the rate at which fructose is removed from the blood is retarded presumably because of some inadequacy of the liver in this respect although such patients need show no other sign of liver dysfunction As a conse quence following the ingestion of fructose or of food containing fruc tose a blood fructose level well above the renal threshold for that sugar is temporarily maintained and fructosuria results As a result of his studies with 3 patients Soisalo[9] stated that in . of them the renal threshold for fructose appeared to lie below a level of 5 to 6 mgm per 100 c c of blood fructose In one normal subject studied by Marble and Smith[10] the renal threshold seemed to be about 11 mgm per 100 c c

The series of the George F Baker Clinic includes only 4 cases 2 males and 2 females all Jews Two of the 4 patients are brother and sister

No treatment is necessary in patients with fructosuria Of impor tance are the recognition of the condition and the demonstration that diabetes is not present

Lactosuria — The commonest type of melituria not due to glucose is that of lactosuria Lactose appears in the urine during lactation it does not appear during pregnancy itself except during the last days The

50 to 60 C for ten minutes The test can with profit be further elaborated by timing the appearance of first evidences of reduction since pentose reduces somewhat more swiftly than does fructose

(2) *Fermentation with Baker's Yeast* — Glucose and fructose are always galactose usually, lactose occasionally and pentose never fermented by baker's yeast The amount of sugar in the urine is determined quantitatively before and after incubation with yeast

(3) *Bial's (Orcinol-HCl) Test* (positive for pentose) — Bial's reagent has the following composition

Orcinol	1 5 grams
Fuming HCl	500 grams
Ferric Chloride (10 per cent)	20 to 30 drops

To 5 c c of the reagent in a test tube add 2 to 3 c c of urine and heat the mixture gently until the first bubbles rise to the surface Either immediately or upon cooling if the test is positive the solution becomes green and a flocculent precipitate of the same color may form

(4) *Seliwanoff's (Resorcinol-HCl) Test* (positive for fructose) — This test is carried out as follows Place in a test tube equal quantities (2 or 3 c c) of urine and 25 per cent hydrochloric acid Bring to boiling over a free flame Add a few crystals of resorcinol and boil actively for 10 seconds If levulose is present almost immediately the solution becomes red and a dense reddish brown precipitate forms This precipitate is entirely soluble in alcohol

(5) The *final procedure* in diagnosis is the preparation of osazone crystals using phenylhydrazine The osazones have characteristic appearances as seen with the microscope and illustrations of such may be found in standard texts The melting point of the crystals is then determined following recrystallization To differentiate between glucose and fructose it is necessary to use methylphenylhydrazine since the osazones of these two sugars prepared with phenylhydrazine are identical The following are the melting points of osazones prepared with phenylhydrazine glucosazone 205 C, pentosazone 157-160 C, the osazone formed by fructose with methylphenylhydrazine has a melting point of 153 C

Pentosuria — Chronic essential pentosuria[7] is a rare hereditary condition which may be regarded as an 'inborn error of metabolism' It is a benign condition characterized by the presence more or less constantly of small quantities of pentose usually xyloketose All reported cases have been in Jews and predominantly in males Pentosuria is

high specific gravity and it seems likely that cane sugar had been added to the urine previously[1]

Summary of Diagnostic Steps

The impression may have been made that the diagnosis of the patient showing sugar in the urine is a complicated and tedious process Such need not be the case From time to time unusual cases will be encountered and these may give the physician difficulty but usually a few simple guiding principles will suffice to establish a satisfactory diagnosis It is important that a plan of action be kept in mind and that diagnosis be settled without delay Delay causes uncertainty and worry for the patient and leaves the physician in doubt as to proper treatment The proper sequence of action in any case should be as follows

(a) Evaluation of the patient s history physical examination and hereditary background

(b) Determination of the amount of sugar in the urine before and after meals and in the blood 45 to 60 minutes after a meal liberal in carbohydrate

(c) In doubtful cases the carrying out of a glucose tolerance test

(d) In cases of persistent meliturua of significant degree despite normal blood sugar values the type of sugar excreted should be determined according to the suggestions outlined in the preceding pages

In any patient in whom there is doubt as to diagnosis or in whom the results of laboratory procedures are equivocal tests should be repeated after a suitable interval Persons showing sugar in the urine persistently should be under the supervision of a physician and have a routine examination at least annually including a determination of the sugar content of the urine and blood

BIBLIOGRAPHY

1 CANTAROW A Melituria Chapter XX Diseases of Metabolism nd Edition edited by Garfield G Duncan W B Saunders Co Phila and London 1947

MARBLE A Treatment of diabetes mellitus in the presence of a high or a low threshold for sugar Med Clin North America 1937 XXI 4 7

occurrence of lactosuria during lactation is a physiological event and requires no treatment

Lactose in urine gives a positive Benedict's test and may be fermented by baker's yeast Tests for the positive identification and determination of lactose are difficult Rules for establishing its presence will be found in standard texts and the articles by Watkins[11] and by Trumper and Cantarow[1] Watkins carried out an extensive study of lactose metabolism in women

Galactosuria — Spontaneous galactosuria is a rare condition of little importance clinically A few cases have been reported, chiefly in children In the case report by Norman and Fashena[13] the suggestion is made that the fundamental defect in this condition lies in the specific enzyme system concerned with the conversion of galactose to glycogen They regard the condition as an "inborn error of metabolism" Patients with galactosuria are characterized by galactosemia, albuminuria, failure to gain and develop normally, anemia and enlargement of the liver and spleen Cataracts may be present Removal of milk from the diet results in the gradual disappearance of abnormalities

Mannoheptulosuria — Blatherwick and associates[11] reported that following the ingestion by 10 normal persons of 136 to 214 gm of avocado mannoheptulose appeared in the urine in amounts from 0 06 to 0 32 per cent This sugar is non fermentable and reduces Benedict's solution in the cold as do pentose and fructose The condition has little clinical importance

Sucrosuria — Sucrosuria or saccharosuria has been reported only rarely and is of little or no importance clinically In the few cases reported in the literature the outstanding feature has been an extraordinarily high specific gravity of the urine In the case of Elmer and associates[1] values up to 1 070 were found and in Hoesch s[16] case the specific gravity was very high ranging from 1 100 to 1 145 The nature of the metabolic defect or error responsible for the condition is not clear Elmer states that the condition occurs in two forms, an exogenous type in which sucrose appears in the liver only after ingestion of cane sugar and an endogenous type in which it occurs independent of the intake of cane sugar Actually however very little is known regarding this rare condition and the physician will do well to be on his guard against possible deception In a case recently seen the urine was found in 8 of 10 office visits to have a specific gravity above 1 050 However, careful observation under hospital conditions did not bear out the finding of a

Chapter VI

DIABETES INSIPIDUS

By HARRY BLOTNER

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4 FOWLER A F Renal glycosuria Ann Int Med 1933 VII 518
5 CORCORAN A C Glycosuria mechanism and evaluation Cleveland Clinic Quart 1948 XV 186
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7 MARBLE A Chronic essential pentosuria A report of three cases Am Jour Med Sci 193. CLXXXIII 827
8 LASKER M ENKLEWITZ M and LASKER G W The inheritance of l xyloketosuria (essential pentosuria) Human Biology 1936 VIII .43
9 SOISALO P Über die essentielle Fruktosurie Acta Soc Med Penn Duodecim, 1933 XIV 1
10 MARBLE A and SMITH R M Essential fructosuria Jour Am Med Assoc 1936 CVI .4
11 WATKINS O Lactose metabolism in women Jour Biol Chem 1928 LXXX 33
1. TRUMPER M and CANTAROW A Clinical interpretation of bio chemical findings — Carbohydrate metabolism Internat Clin 1931 I 38
13 NORMAN F A and FASHENA G J Chronic hypergalactosemia Am Jour Dis Child 1943 LXVI 531
14 BLATHERWICK N R, LAWSON, H W and SAWYER S D Metabolism of d-mannoheptulose Excretion of the sugar after eating avocado Jour Biol Chem 1940 CXXXIII 643
15 ELMER A W KRASOWSKA M and PTASZEK L Sucrosuria A rare metabolic error Acta med Scandinav 1939 CI 596
16 HOESCH K Spontane periodische Rohrzuckerausscheidung Klin Wochnschr 1934 XIII .75
17 MARBLE, A The diagnosis of the less common meliturias including pentosuria and fructosuria Med Clin North America 1947 XXI 313

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INTRODUCTION

Definition — Diabetes insipidus is a chronic disease characterized by marked polyuria thirst and polydipsia persisting during the day and night It is due to a deficient formation of pituitary extract secreted by the posterior lobe of the pituitary gland and is interrelated with the function of the kidneys whereby the reabsorption of water by the kidney tubules is diminished

The name diabetes comes from the Greek signifying a siphon and was given to the affliction in which the patients never stop making water for the flow is incessant as if coming from a fountain It was differentiated in early days from diabetes mellitus by the insipid or flat taste of the urine in contrast to the sweet taste of the urine in patients with diabetes mellitus

sent as if from the opening of aqueducts Hence this disease appeared *to Aretaeus to have derived the name diabetes as if from the Greek word* signifying a siphon because the fluid does not remain in the body but used the man s body whereby to leave it

In discussing the cause of diabetes Aretaeus said The cause of it may be that some one of the acute diseases may have terminated in this and during the crisis the diseases may have left some malignity lurking in the part It is not improbable also that something pernicious derived *from the other diseases which attacked the bladder and kidneys may* sometimes prove the cause of this affection but if any one is bitten by the dipsas which is a species of viper the affection induced by the wound is of this nature for the reptile the dipsas if it bite one kindles an unquenchable thirst For they drink copiously not as a remedy for the thirst but so as to produce repletion of the bowels by the insatiable desire of drink

Nothing definite can be *determined* respecting the age in which Aretaeus lived beyond an approximate period From various investigations and deductions he appears to be a contemporary of Galen It is singular that neither Galen nor Aretaeus considering their eminence as professional authorities and the fact that they were both voluminous writers ever made the slightest allusion to each other Yet one can detect a decidedly corresponding coincidence between their literary and professional views A mutual feeling of rivalry has been suggested as an explanation of their behavior

Sir Thomas Willis[3] in 1674 1684 was credited by some as the first to differentiate diabetes mellitus from diabetes insipidus by his description of the urine However in a perusal of his publications in Latin and *in English I could find nothing to indicate that he had described or had* known there was such a condition as diabetes insipidus

Thomas Willis did describe in part the urine of the pissing disease or diabetes as follows For this reason it does not seem improbable that this sweetness is obtained from these rich juices mixed with a fluid *Assuredly* it is true that from this mixture a taste quite mild and in appearance either like milk or juices of meat gently smooth (bland) but not honey sweet (mellitus) is brought out Certainly the descriptions of these urines do not suggest diabetes insipidus

Cullen[4] in 1789 first used the names diabetes insipidus and diabetes mellitus when he described two types of diabetes namely one with a honey taste to the urine (diabetes mellitus) and one with a tasteless urine

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Diabetes insipidus is one of the most fascinating diseases in medicine to study and treat. It is a part of that great field of endocrinology, which in recent years has shown great advances. Although diabetes insipidus is seen rarely, the large number of papers on this subject, out of proportion to the incidence of the disease, illustrates the absorbing interest this disease has for investigators. I have seen or studied 112 patients with diabetes insipidus, 32 of them closely for periods ranging from 5 to 20 years. Many studies have been made as a result of their cooperation.

Since treatment with solution of posterior pituitary was introduced, diabetes insipidus is not a harmful or uncomfortable disease. Diabetes insipidus of idiopathic origin or following some infection is a hopeful disease. Such patients may expect to live a normal life and plan useful careers. It is the purpose of this chapter to present the history and the advancement in knowledge of this disease as well as to describe my experiences in this field.

History

Diabetes insipidus has had a varied nomenclature. It has been referred to in such terms as polyuria, polyuresis, diuresis, polydipsia, hydruria, essential polyuria, diabetes spurious, habitual diuresis and hyperuresis.

There is some question as to who was the first to describe diabetes insipidus or to use the word diabetes. However, Galen[1] who was born about 131 A.D. and Aretaeus, the Cappadocian, a contemporary of his, both used the word diabetes in their writings. In his discussion of diabetes Galen believed that the kidneys suffered from this rare disease, variously called dropsy into the pot, diarrhea of the urine, diabetes and the thirsty disease. It is quite possible that Galen had observed two instances of diabetes insipidus for he said, 'I have seen only two cases in both of which the patients suffered excessive thirst and for this reason drank copiously and passed in the urine immediately as much as they had drunk. This disease is similar also in the kidneys to lientary in the bowels. Those that blame the stomach for the excessive hunger and thirst as well as the disease diabetes are wrong as found by the fact that the thirst continues even after the stomach is filled with fluid.

Aretaeus, the Cappadocian, described the unquenchable thirst, the excessive drinking and the large quantity of urine in diabetes. He commented: 'The course is the common one, namely, the kidneys and the bladder; for the patients never stop making water, but the flow is inces

to her former quantity of three pailfuls and continued it till after the birth of her fourth child Since that period she has drank only two pailfuls in the four and twenty hours When she is sick she has no longer the same thirst, and when she does not drink as much as she desires, she is ill When she lays in she has much more thirst than usual She has more thirst in summer than in winter

Salted meats she is not fond of eating but they do not render her more thirsty than other aliments Her thirst occasions a sensation at the stomach similar to that which is excited by hunger Her mouth is clammy, and she is unable she says to swallow a bit of bread

When she has drank she feels about the region of the stomach a pretty considerable coldness which occasions her to shiver for some time and obliges her to be constantly near the fire whenever the weather happens to be at all cold

This woman has the lower lip rather thick and covered with scabs This lip smarts and at times is very painful to her especially in summer She is subject to the blind piles and when these take place the complaint in her lip ceases

She has had eleven children in ten lyings in It is since the birth of her first child that she has been subject to the piles Of all her children there remains only two Almost all of those she has suckled have been subject to different diseases Her eldest who is still living had a disease of the skin similar to the itch but which is not infectious Her youngest child which she has suckled only a month is in very good health

This woman is the only one of her family who has so great a thirst She perspires sufficiently and her urine is in proportion to what she drinks She does not spit She drinks neither wine nor coffee nor spirituous liquors She told us that she ate a great deal but we did not observe this while she was with us

This woman drank in our presence during the space of ten hours which she remained with us fourteen quarts (or Paris pints) of water which must be equal to about twenty eight pounds She assured us that in the night time she rises every hour and a half to drink and this will be found to make pretty exactly the load or two pailfuls of water which this woman asserts that she drinks in four and twenty hours

She voided ten quarts of urine that was nearly colourless

M M Bonnard Lair and Robilliard members of the Philomatical Society observed with us this woman during a considerable part of the day

(diabetes insipidus) In the first the urine had a honey odor, taste and color, in the second the urine on the contrary was very pale and not sweet He also described the polyuria of hysteria and a true idiopathic polyuria with a tasteless urine which was very rare

An excellent description of diabetes insipidus without mention of its name was included in an early medical book "Medical Facts and Observations," edited by Dr Simmons in 1792 This report relative to a woman who drinks a great quantity of water originally was presented by M M Bellot and Brougniart[5] on the 22nd of October 1791, to the Philomatical Society The picture given is so complete and interesting that this study deserves to be quoted in detail

The Philomatical Society, being desirous of complying with the request made by M Parmentier, in the name of Dr Simmons, appointed us to examine the temperament and habits of a woman who drinks a great quantity of water

"We accordingly went on Saturday, the 15th of October to the woman in question, at the Hotel des Arts Fauxbourg, St Martin Not having met with her at home, we went from thence to the place where her husband was at work having previously collected from the porter of the hotel several points of information which agreed with what had already been told to us We found the woman with a pitcher of water by her side, and a day being appointed for the purpose, it was settled that she should come and pass the whole of it with us

"We met accordingly on Monday the 17th of October 1791 and received from this woman the following particulars Catherine Bon sergent wife of James Fery a cobbler now living in the Hotel des Arts Fauxbourg St Martin parish of St Lawrence, at Paris is forty years old and was born at Senlis

She is very fair, her skin is fine but freckled She is rather lean than fat, and seems to be of a bilious temperament Her arms are leaner than the rest of her body

"At the time she was weaned she was placed with her grandmother who drinking a good deal of wine made her also drink it When she returned home to her mother she vomited up everything she took What she vomited was of a black colour

"From her earliest infancy she had a very considerable thirst and sought every means of satisfying it While she was single, she drank three pailfuls of water a day, after she was married two pailfuls were sufficient for her till she was delivered of her first child, she then returned

to her former quantity of three pailfuls and continued it till after the birth of her fourth child Since that period she has drank only two pailfuls in the four and twenty hours When she is sick she has no longer the same thirst and when she does not drink as much as she desires she is ill When she lays in she has much more thirst than usual She has more thirst in summer than in winter

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While the preceding account was being prepared for the press, the following paragraph[5] appeared in the Lincoln Mercury of Friday, December 9, 1791

However extraordinary the following circumstances may appear, it may be depended on as fact — A man, who lives with Mr John Julyan of Woodstone, near Peterborough, is afflicted with such an immoderate degree of thirst, as obliges him to drink the astonishing quantity of three gallons of water a night, and one gallon a day, and what makes this appear still more extraordinary, he has continued this practice twenty three years'

Consequently this man was investigated The truth of the facts are given in an extract of a letter to Dr Simmons dated Fletton Lodge near Peterborough December 18, 1791

With respect to the water drinker, who is the subject of your inquiry and who lives at Stanground near Woodstone though he works at the latter place it happens that Mr Beal the person who now looks after my farm, employed him as a thrasher more than twenty years ago

"His account of this man is that he always drank the quantity that he is now said to do, or at least was at that time reputed to drink it As he resided three or four miles from Mr Beal's habitation the latter used to make up a bed for him in his house and Mr Beal observed that at night he always took a bucket full of water upstairs with him

I have a laborer likewise who has worked with him, and who says in mowing time this man always takes four quarts of water out with him from a pump in the village besides two quarts of beer

This man adds that he has consulted several medical gentlemen about his complaint but has not been able to get anything that could in the least relieve him"

Johann Peter Frank[6] in 1797 and 1832 subdivided diabetes into various types In one type the urine was copious, watery and had an insipid taste In another type the urine was sweet as though mixed with honey He described the case of a man in his clinic who had for some years a daily urine volume of 40 pounds which on one day reached 5 pounds

Another type of classification was suggested by Robert Willis[7] in 1838, who classified diabetes insipidus according to the excretion of urea, 1 hydruria in which the discharge of urine is characterized by deficiency of solid matters generally but with a normal excretion of urea 2 anazoturia in which the polyuria is characterized by a deficiency

of urea elimination 3 azoturia in which there is a polyuria with a superabundance of urea

Although the earlier writings had suggested that the diabetes was due to a disease of the kidneys it was not until 1855 that the renal origin of diabetes insipidus seemed to acquire foundation and that the experimental phase of the cause of diabetes insipidus commenced At this time Claude Bernard[8] punctured the floor of the fourth ventricle which he interpreted as a center in the brain for the control of kidney secretion His so called diabetic center was situated in the floor of the fourth ventricle Puncture of this center in dogs caused glycosuria Puncture a little lower caused polyuria This work confirmed by Eckhard[9] and Kahler[10] led to the conclusion that the polyuria of diabetes insipidus was due to nervous excitation of the kidneys The impulses were believed to originate in the brain as a result of injury or tumor and were transmitted to the kidneys by nerve fibers which left the cord in the uppermost thoracic region and passed to the kidneys along the walls of the aorta and renal arteries This theory was disclaimed by some physiologists Nevertheless it was not until 1921 that it was refuted finally by Bailey and Bremer[11] These authors denervated the kidneys of a dog with diabetes insipidus and observed not only the absence of urinary suppression but actually an increase of the polyuria by the denervation polyuria

Another theory for the renal origin of diabetes insipidus was suggested by a number of investigators[12] who interpreted the results of their studies on the action of the kidneys in diabetes insipidus as indicating primary inability of the kidneys to concentrate urine The urine therefore was of low specific gravity and concentration the excretion of added sodium chloride in the diet resulted in an increased polyuria thus maintaining the same degree of dilution of sodium chloride in the urine This theory was discarded finally because it was demonstrated[13] later that the kidneys of patients with this disease could concentrate urine

Investigations have shown since the discovery of the antidiuretic principle that the kidneys are involved secondarily in diabetes insipidus Due to a deficient pituitary secretion the kidney tubules are unable to reabsorb water and as a result large amounts of urine are excreted The details of the renal function illustrating this phenomenon in diabetes insipidus will be discussed in the section on physiology

The history of diabetes insipidus relating to the hypothalamus and

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in a 37 year old woman Two months after excision of the breast for a carcinoma she developed a marked polyuria and polydipsia The autopsy showed a metastasis which destroyed the posterior lobe of the hypophysis and pressed on the pars intermedia without involving it or the anterior lobe

Following these reports numerous similar cases began to appear in the literature confirming this relationship

Additional support was given to the involvement of the posterior lobe by the reports in 1913 of von den Velden[2] and Farini[3] who working independently demonstrated that the hypodermic injection of pituitrin had a marked effect in reducing the polyuria and polydipsia in this disease As a result of this evidence it was quite natural that the view that diabetes insipidus was due to disturbed function of the posterior lobe of the hypophysis should have gained rather general acceptance

While the hypophyseal idea of the cause of diabetes insipidus was gaining ground experimental work appeared casting some doubt on it and indicating that the lesion was not in the posterior lobe but in the hypothalamus

The hypothalamus or mid brain forms the floor of the third ventricle It consists essentially from before backwards of the optic chiasm the tuber cinereum and corpora mamillaria In addition there is the infundibulum situated below the tuber cinereum and terminating in the infundibular stalk which is attached to the upper surface of the posterior lobe of the hypophysis

The question of relationship between polyuria and experimental lesions of the hypothalamus in dogs was undertaken first by Camus and Roussy[4] in 1913 These investigators succeeded in producing transitory polyuria by puncturing the hypothalamus of dogs the polyuria being due to injury to the tuber cinereum In 19 0 they stated that this phenomenon did not depend on a lesion of the pituitary gland because complete removal of the pituitary gland did not result in polyuria unless the base of the brain was injured

Bailey and Bremer[11] in 19 1 confirmed the views of Camus and Roussy[4] that injury to the hypothalamus in addition to causing polyuria also in some instances resulted in the production of an adiposogenital syndrome which has been supposed to be dependent on pituitary disturbance

the hypophysis is of more recent date. The earlier experiments along these lines were confusing chiefly because Magnus and Schafer[14] in 1901 and Schafer and Herring[15] in 1905 reported that the extracts of the posterior lobe of the hypophysis had a diuretic effect in the anesthetized animal.

This misconception influenced early theories of the etiology of diabetes insipidus. For example Frank[16] in 1910 was the first to present clinical evidence that injury to the hypophysis could cause diabetes insipidus but made the improper conclusion that it was due to irritation and hypersecretion of the posterior lobe of the pituitary gland.

Investigations of the cause of diabetes insipidus became more active after that period. The following views in order have been summarized by Futcher[17]: 1, that it is caused by a disturbed function of the posterior lobe of the hypophysis, 2, that it is produced by organic changes involving one or more of the structures comprising the hypothalamus, 3, that there is a center, the nucleus supraopticus or nucleus paraventricularis, located in the hypothalamus near the floor of the fourth ventricle that presides over the normal water metabolism, that nerve fibers originate in this center and pass down through the hypothalamus and infundibular stalk and spread throughout the entire posterior lobe and even between the cells of the pars intermedia and that a lesion involving any part of this tract, the tractus supraoptico-hypophyseal, so disturbed water regulation that diabetes insipidus results. The relative value of these theories will be reviewed briefly.

For some years following 1910 the theory that diabetes insipidus was dependent upon lesions of the hypophysis prevailed. Cushing and his associates[18] at that time reported the results of the removal of the posterior lobe in dogs and found that this operation often was followed by transitory polyuria. In 1913 Cushing[19] stated that polyuria had been so marked in 6 of his first 100 cases of pituitary disease that it led to a diagnosis of *diabetes insipidus by the physicians who referred these* patients.

The first clinical report showing the relationship between diabetes insipidus and lesions of the hypophysis was made in 1912 by E. Frank.[9] He described a man who had been shot and was found by x-ray to have a bullet lodged in his sella turcica. This is a detailed report of the briefer one he gave in 1910[16].

In 1913 and 1914 M. Simmonds[1] reported a case of diabetes insipidus

of greatest importance They found that in the nucleus supraopticus and nucleus paraventricularis situated on each side of the medium line near the floor of the third ventricle and adjacent to the optic chiasm nerve fibers arise forming a definite bundle which passes down on each side near the tuber cinereum through the infundibulum and infundibular stalk into the posterior lobe Where they form an extensive network and surround groups of cells which are thought to form the secretion of the posterior pituitary lobe Some of these fibers also can be traced between the cells of the pars intermedia Greving called this tract of nerve fibers beginning in the nucleus supraopticus and terminating in the posterior lobe the supraoptic hypophyseal tract The conception was that the nucleus supraopticus was the center that presides over the normal regulation of water balance

Zadek[39] suggested that lesions anywhere along this supraoptic hypophyseal tract may produce diabetes insipidus The discovery of this tract goes a long way towards reconciling the conflicting views of the pituitary and hypothalamic adherents Futcher[17] conjectured that tumors or other lesions involving the nucleus supraopticus the posterior lobe of the hypophysis or the tract anywhere between these 2 points may produce diabetes insipidus

Although the anterior lobe of the pituitary gland is known to have a diuretic principle there has been comparatively little experimental work done on this lobe in relation to diabetes insipidus On the other hand there has been a considerable number of publications on the relationship between the thyroid and the pituitary gland water balance and the fluid intake and output in diabetes insipidus[31] This literature goes back as far as 1889 when Rogowitsch[3] found alterations in the pituitary gland of thyroidectomized animals

Finally Fisher Ingram and Ranson[33] in 1938 published their enlightening monograph which deals with extensive experimental investigations on animals and throws considerable light on the complex nervous and hormonal factors involved in the regulation of water balance and on the cause of the great increase in water exchange which occurs in diabetes insipidus

In spite of the considerable literature on diabetes insipidus there have been heretofore no autopsy findings in human beings who have had diabetes insipidus of idiopathic origin for many years In this publication there are the pathological reports of 2 such cases along with others which help clarify the cause of this disease

From the clinical standpoint there was evidence that diabetes insipidus in man could be produced by hypothalamic lesions Lrdheim in 1904 suggested as a result of clinical and pathological studies that the polyuria associated with organic brain disease was actually dependent upon tumors or other lesions involving the hypothalamus In 1919 Christian[6] published his classical findings on xanthomatosis which is associated with a lipoid disturbance in various organs and tissues in the body producing in some cases diabetes insipidus

In 1928 Llmer, Kedziersk and Scheps[27] reported a case of diabetes insipidus in a patient with hypernephroma of the kidney with a metastasis in the hypothalamus An embolus of the hypernephroma cells had blocked an artery causing a necrosis of the tuber cinereum Futcher[10] in 19 9 published the records of a case of diabetes insipidus in a man who had a primary carcinoma of the lung with a metastasis about 1 5 cm in diameter involving the infundibulum and tuber cinereum with an intact pituitary gland

These reported cases seemed to produce highly conclusive evidence that diabetes insipidus could be caused clinically and experimentally by lesions involving the structures comprising the hypothalamus without any involvement of the posterior lobe of the pituitary gland The suspicion began to arise that, when the clinical picture of diabetes insipidus occurred in growths involving the posterior lobe as well as in the case of hypophyseal duct cysts the cause of polyuria and polydipsia was actually due to a pressure on the structures comprising the hypothalamus The intense thirst and polyuria, that not infrequently *follow* the attempt of surgical removal of basilar tumors in the region of the hypophysis might be explained in a similar way

From the foregoing it may seem that there are the hypophysis and the hypothalamus proponents of the cause of diabetes insipidus In recent years the adherents of the hypothalamus conception have been getting rather the better of the argument

It now remains to present the evidence which tends to show that the adherents of both groups are right in their interpretation Greving[8] and Pines[9] in 1926 studied the cause of diabetes insipidus by attacking the problem from the standpoint of determining whether there were any demonstrable nerve paths originating at any particular point in the hypothalamic region and communicating with the posterior lobe Working independently they made a contribution to this problem which is

tion of the cavity of the tuber cinereum and is thus part of the third ventricle

The gland itself lies within a recess in the sphenoid bone known as the sella turcica The floor of this bony hollow forms the roof of the sphenoidal sinus and its four corners are elevated to form two anterior and two posterior clinoid processes The sella turcica is lined by dura mater and is roofed almost completely by a fold of the dura the diaphragma sellae The hypophyseal stalk passes through an opening in this membranous roof

In close proximity to the pituitary gland on both sides are the third (oculomotor) fourth (trochlear) ophthalmic division of the fifth and the sixth (abducens) nerves Just above and in front of the pituitary and separated from it by the diaphragm sellae is the optic chiasm The relative location of these structures is of clinical importance in considering pressure effects from pituitary gland enlargement and in explaining the frequent visual disturbances in cases of pituitary tumor

The human pituitary gland is described generally as consisting of two lobes an anterior and a posterior The anterior lobe is much the larger of the two and its posterior aspect is hollowed out so as to fit like a cap over the posterior lobe In other words the posterior lobe rests in the hollow of the anterior portion like a ball within the palm of the hand On section the anterior lobe is soft but tough in consistency and yellowish pink The posterior lobe on the other hand is very soft and nearly white In addition there is the pars intermedia an important structure which forms a thin layer surrounding the posterior lobe and is separated from the anterior lobe by a narrow interglandular cleft

The supraoptic hypophyseal system which originates in the supraoptic nucleus and other anterior hypothalamic nuclei forms an anatomical and functional unit The supraoptic nucleus lies immediately above the optic chiasm at the anterior end of the optic tract It projects for a short distance along the anterior aspect of the tuber cinereum This nucleus is of special interest physiologically and pathologically because it gives rise to the supraoptic hypophyseal tract which runs through the median eminence and the central walls of the infundibulum stem to form a meshwork in the pars nervosa Much of our modern knowledge of diabetes insipidus is dependent on this system

The corpora mammillaria each about the size of a small pea are two round white masses placed side by side and behind the tuber cinereum

The tuber cinereum is a hollow rounded eminence of gray substance

Anatomy of Pituitary Gland and Associated Structures

It is well to have a clear conception of the general anatomy of the pituitary gland and its associated structures to understand the physiology and pathology of diabetes insipidus (see Fig 1)

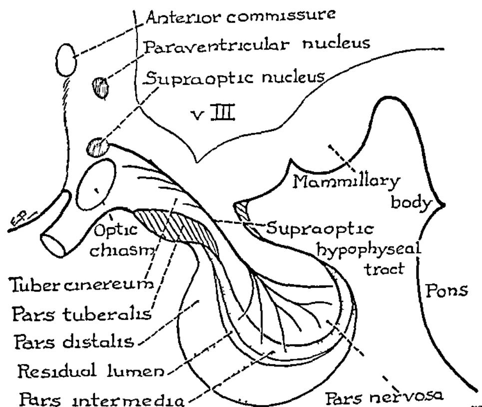


Fig 1 Diagram showing a sagittal section of the pituitary gland and the supraoptic hypophyseal tract

The hypothalamus includes the subthalamic tegmental region and the structures forming the greater part of the floor of the third ventricle These structures are the corpora mammillaria tuber cinereum infundibulum hypophysis and optic chiasma

The pituitary gland is an oval slightly flattened reddish gray body of tissue situated at the base of the brain It measures about 1- 5 mm in transverse and 8 mm in anterior posterior diameter It is attached to the end of the infundibulum a funnel-shaped stall which extends downward from the tuber cinereum The cavity of the infundibulum is a prolonga

Physiology

The physiology of diabetes insipidus may be considered under four headings as follows (1) mechanism of thirst (2) renal function (3) pituitary gland (4) other endocrine glands

Mechanism of Thirst

The mechanism of thirst ordinarily is considered to be the result of a general sensation arising in some way from the loss of water which results in desiccated tissues Cannon[35] explained the normal thirst on the basis of a local sensation resulting from dryness in the mucous membranes of the mouth which is due to decreased secretion from the salivary glands This in turn was dependent on the diminished supply of fluid furnished these glands by the body because of its depletion in water Cannon further stated that the osmotic pressure of the blood remained unchanged despite deprivation of fluids in tissues Dehydration of all tissues including the salivary glands led to diminished secretion of water by these glands Normally the salivary glands furnish the index of the body need for water

Thirst and dry mouth are striking symptoms of patients with diabetes insipidus There is a very small amount of saliva secreted in untreated patients with diabetes insipidus On the other hand the secretion of saliva is increased markedly following the administration of pituitrin The details of this phase are discussed elsewhere under the heading Mouth Saliva and Teeth In diabetes insipidus there appears to be a primary disturbance of the normal water distribution in the body so that the water which should be stored in various tissues is excreted and leads to a shortage of water in the system However if there is a disturbance in the normal water distribution in the body of patients with diabetes insipidus it has not been demonstrated by blood volume changes hematocrit readings red blood counts or blood chloride and blood protein determinations This holds true for any other analyses that we have been able to make Possibly the changes in the blood and body fluids are too small to be able to be detected by the methods that we have on hand at present although there may be sufficient changes in the blood to produce a sensation of thirst

That the mechanism of thirst is not the primary cause of diabetes

situated in front of the corpora mammillaria and behind the optic chiasma From the under surface of the tuber cinereum a hollow conical process, the infundibulum, projects downward and forward and is attached to the posterior lobe of the hypophysis It is pressed forward against the optic chiasma

Embryologically the subdivision of the pituitary gland varies somewhat from its simple morphologic subdivision Developmentally the gland consists of an oral or epithelial portion and a neural portion These do not coincide precisely with its gross anterior and posterior lobes because the posterior lobe consists of all the neural portion plus some of the epithelial portion

In fetal life a dorsal outpocketing of the oral epithelium known as Rathke s pouch, appears just anterior to the pharyngeal membrane This outpocketing pushes progressively upward to meet an evagination from the hypothalamic region of the brain As Rathke s pouch advances toward the neural epithelial evagination its attachment to the oral epithelium becomes constricted to an epithelial stalk Later the pouch becomes separated from its stalk and proceeds to develop into the anterior lobe the residual cleft and the pars intermedia of the pituitary gland

After Rathke s pouch becomes pinched off from its stalk its ventral aspect begins to grow much thicker and the other quite thin This glove like structure now wraps itself partially around the neural evagination so that the neural lobe rests in the hollow of this structure The neural evagination has become thickened at its tip to form the infundibular body or pars nervosa of the hypophysis, and it has become narrowed proximally to form the infundibular stalk The thin posterior surface of Rathke s pouch becomes adherent to the pars nervosa so that the structure now appears to be composed of two lobes separated by a cleft which is the residual lumen of Rathke s pouch What appears to be the anterior lobe represents only part of the original epithelial outpocketing What appears to be the posterior lobe represents all of the neural evagination plus the thin epithelial wall of the oral evagination This thin epithelial layer adherent to the neurohypophysis is known as the pars intermedia In addition two buds develop from Rathke s pouch and grow up along the infundibular stalk to form the pars tuberalis which remains relatively small

The anatomy of the pituitary gland is described by Friedgood in detail in Vol III Chapt XIV of the Oxford System of Medicine[31]

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insipidus may be illustrated by the fact that cocainization of the mucous membranes of the mouth and nasopharynx of patients with this disease fails to control their marked polydipsia and polyuria. That a dry mouth is not a primary factor in diabetes insipidus is illustrated by cases of xerostomia, a condition characterized by suppression of the secretion of the salivary and buccal glands: dry oral mucous membranes and no polydipsia or polyuria. Gregersen's[36] research indicated that thirst in diabetes insipidus is due to dehydration as a result of the polyuria.

The question of whether the polyuria is simply the result of primary polydipsia or vice versa has not been answered absolutely. In some of my cases of diabetes insipidus thirst, which led to polydipsia, appeared to be the first symptom of the disease. On the contrary, polyuria occurred first in some instances with secondary thirst and ingestion of large quantities of water. In some patients thirst, polydipsia and polyuria appeared to occur simultaneously and suddenly, and in other cases simultaneously and gradually.

There has been experimental work on animals concerning this problem. Richter[37] indicated that the polyuria was primary in animals in which diabetes insipidus was produced by hypophysectomy or a stab wound in the floor of the third ventricle. The polyuria preceded the polydipsia, and the animals deprived of water continued to excrete large quantities of urine. On the other hand Bellows and VanWagenen studied the relationship of thirst, polydipsia and polyuria of experimental diabetes insipidus by means of esophageal fistulae in dogs and came to the opposite conclusion. In such dogs diabetes insipidus was produced by appropriate hypothalamic injuries. The water of thirst which was discharged uningested from the esophageal fistula afforded an objective measure of the degree of thirst.

Diabetes insipidus produced in a dog with an esophageal fistula which received a normal amount of water intake resolved itself into the single factor of polydipsia, and the urinary output appeared to be secondary at all times to the actual water intake. In the fistulous dog it corresponded in time relations and magnitude to the polydipsia of non-fistulous dogs. The fistulous dog appeared to suffer no ill effects from being deprived of the water which the non-fistulous dog obtained. Polydipsia, therefore, they considered to be the primary factor in diabetes insipidus.

The production of a persistent thirst or primary polydipsia by an injury to the hypothalamus suggested that this region of the brain is the

center of the thirst function Since diabetes insipidus appears to be fundamentally a disturbance in water metabolism the thirst function thereby appears to be an integral component of the mechanism which controls the water metabolism Thirst therefore may be regarded as the activity of a mechanism in the central nervous system due to variations in either the water or the solute content of the body

As the result of the various studies which have been made thirst in diabetes insipidus is more than just an expression of dryness of the oral mucous membranes and lack of salivary secretion

Renal Function in Diabetes Insipidus

Various kidney function tests had been made in many of our patients with diabetes insipidus Analyses of the blood such as the amount of non protein nitrogen blood urea nitrogen blood uric acid and creatinine have shown normal figures The phenolsulfonephthalein excretion was normal In fact the results in most cases showed a high excretion of the dye during the test periods

The specific gravity of the urine in this disease when untreated usually ranges from 1 000 to 1 003 Comments have been made on the inability of these patients to concentrate urine I have seen the urine concentrated to a specific gravity of 1 01 and 1 016 when the fluid intake had been restricted markedly and also during fever with restriction of fluids The chief reason for not obtaining concentrated urine is that there is great difficulty for these patients to restrict markedly the fluid intake

In general careful studies of renal function in diabetes insipidus have shown one appreciable and important abnormality and this relates to the reabsorption of water in the kidney tubule It is the most important mechanism in diabetes insipidus except for that of the pituitary gland Diabetes insipidus is a bilateral renal condition as shown by the fact that when the ureters are catheterized the increased secretion of urine is bilateral and the same on both sides Tests of renal function have been performed under conditions of pituitary deficiency The knowledge of this phase of renal behavior is essential to an understanding of diabetes insipidus and its relation to the administration of pituitary extract

Various methods of investigation[5] have been used for kidney function in diabetes insipidus For example Schmitz[1] found a creatinine

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a reduction in glomerular filtration as measured both by creatinine and by inulin clearance in hypophysectomized dogs

On the basis of the studies which were presented by them it was reasoned that if the inulin clearance is known to be the same in both phases the filterable fraction of diodrast must also be the same so that whatever variations do occur in effective plasma clearance must be attributed to the tubule cells It might be suggested that the decrease in plasma clearance is due to an impairment in the excretory function of the tubule cell which is restored under the influence of repeated administration of solutions of posterior pituitary The administration of solution of posterior pituitary producing an acute transition from diuretic to antidiuretic phase was accompanied by a sharp drop in the glomerular filtration rate and in the renal plasma flow with a rise in the filtration fraction The acute effect subsided within 15 to 20 minutes with the plasma flow in 3 of 5 cases eventually reaching a level above that of the control period The effect is believed due to a predominant constriction *of the efferent arterioles possibly extending to the afferent arterioles*

The study of the relation of renal plasma flow and glomerular filtration to urine output during the course of progressively increasing diuresis with corresponding loss of the antidiuretic effect of posterior pituitary extract revealed their independence of one another This offers corroboration for the hypothesis that excretion of water is a function of tubular reabsorption

That the function of reabsorption of water by the kidney tubules is disturbed in diabetes insipidus and may be corrected with the administration of pituitrin has been shown also by experimental procedures in which pituitrin and its effect on the kidney have been studied in mammals and amphibians Starling and Verney[12] have found that pituitrin acts directly on the kidney in producing antidiuresis with characteristic changes in the urine This interpretation was supported by the results of Janssen[13] who showed that the direct injection of pituitary extract into the renal artery of one kidney produced a response in that kidney before a similar response occurred in the opposite kidney The effect was produced despite the ruling out of a nervous mechanism by section of the spinal nerves between the fifth and sixth cervical vertebrae and double vagotomy Others have corroborated these results[14]

Addis and associates[15] postulated more specifically that the inhibitory effect of pituitary extract was due to its specific action on the secreting cell of the kidney Positive evidence, especially for the proximal portion

clearance in 4 cases to be normal and concluded that the polyuria was due to a failure in tubular reabsorption of water White and associates[40] studied renal function in dogs in which the pars nervosa of the pituitary gland and the accessory sites of pitressin production had been removed Within 2 to 4 weeks after operation they noted a fall both in urea and in creatinine clearance of from 30 to 50 per cent with a return to normal after several months In other experiments the fall in urea clearance was less than that of creatinine clearance Later they measured the inulin and diodrast clearances in hypophysectomized dogs and found the results to be one half that in normal dogs The diodrast plasma clearance after operation showed an average decrease of more than 40 per cent with an approximately corresponding drop in the renal plasma flow Both the plasma diodrast extraction determined from blood drawn from the renal vein and tubular diodrast extraction remained constant in the normal and in the hypophysectomized animals The glomerular filtration rate decreased correspondingly with the drop in renal plasma flow while the filtration fraction remained unchanged The total excretory mass after hypophysectomy was found to be decreased by more than 50 per cent

Winer[41] presented a review of the literature on renal hemodynamics water exchange and the relation of both to the pituitary and made a study on the state of renal blood flow and glomerular filtration in 7 of our cases of diabetes insipidus under certain conditions The problem of renal function in human diabetes insipidus was approached with the inulin and diodrast clearance tests with the idea of establishing the site of pathological function of the kidney The comparison of function during the well established diuretic phase with that during the antidiuretic phase revealed a decrease in effective plasma clearance in the diuretic phase in most instances from 20 to 60 per cent below clearance during the antidiuretic phase This did not tend to be true, if the diuresis was of short duration The glomerular filtration rate as measured by inulin clearance, and the total excretory mass were relatively constant in both phases indicating the absence of any glomerular mechanism in the pathogenesis of diabetes insipidus as well as the independence of glomerular filtration and urine output in general This finding is in complete accord with the studies in diabetes insipidus by Schmitz[39] but not with the animal experiments of White and associates[40], if their studies may be placed on a comparable basis The last named authors reported

These data suggested that at least three separate mechanisms one controlling water excretion (posterior pituitary) one controlling sodium excretion (adrenal cortex) and certain intrinsic renal adjustments may be involved in the antidiuretic responses to venous congestion of the limbs and that the participation of the splanchnic sympathetic nervous system is not necessary Further evidence in support of these concepts has been obtained recently in normotensive and splanchnicectomized hypertensive subjects under a large osmotic (mannitol) diuresis In these experiments venous congestion of the limbs caused no appreciable change in urine flow although it resulted in the normal decrease in sodium excretion

Other comments on renal function in relation to the pituitary gland will be discussed further under the next heading Physiology of the Pituitary Gland

Physiology of Pituitary Gland in Relation to Diabetes Insipidus

Posterior Lobe of Pituitary — Diabetes insipidus is a hormonal disturbance due to a deficiency in the production or secretion of the antidiuretic principle of the posterior lobe or the neural division of the pituitary gland It represents a nerve disturbance because lesions of the hypothalamus and the supraoptic hypophyseal tract result in changes in the hypophysis Ranson and associates[33] have shown that extirpation of the neural division or its atrophy due to interruption of the supraoptic hypophyseal tract resulted in a marked diminution or abolition of the antidiuretic hormone in the organism and a subsequent diabetes insipidus This was demonstrated in polyuric cats by assaying the atrophic pituitary glands which were found to contain practically no antidiuretic substance The control tests on normal pituitary glands gave a normal antidiuretic response

In diabetes insipidus there appears to be a marked diminution or abolition of the antidiuretic principle of the neural division of the pituitary gland The evidence in favor of a deficiency theory of diabetes insipidus is corroborated also by the well known fact that extracts of the neural division of the pituitary gland control the polyuria and polydipsia of diabetes insipidus Lesions of the hypothalamus which resulted in atrophy of the neural division produced diabetes insipidus Not only the secretion of the antidiuretic principle was under the control of the

of the tubule as the site of antidiuretic action was proposed by Poulsson[11] on the basis of the effect of pituitary extract on urea excretion Gersch and Stieglitz[1] and Gersch[13], using the ferrocyanide method, stipulated that the loop of Henle and less so the proximal convolutions was the site of action of pituitary extract Burgess Harvey and Marshall[19] made some ingenious zoological studies of antidiuretic response and the site of antidiuretic action of pituitary extract They observed that the antidiuretic action of pituitary extract in the man, dog and bird was due to an increased water reabsorption by the kidney tubule but found no antidiuretic effect in the amphibian or in the fish because they do not have a loop of Henle Since a typical antidiuretic effect was present only in mammals that have a loop of Henle they concluded that the antidiuretic effect of pituitary extract in man and other mammals was due to a stimulation of water reabsorption by a thin segment of the loop of Henle It appears from these various experiments that the loop of Henle is the site of physiological deficiency in diabetes insipidus which is corrected when pituitary extract is administered

Wilkins and associates (461) recently have made some unique experiments on the effect of venous congestion of the limbs on the hemodynamic and renal functions in patients with diabetes insipidus In previous experiments Wilkins and associates (462) observed that venous congestion produced by inflation of blood pressure cuffs to less than diastolic pressure on the thighs of normal and hypertensive patients usually caused a marked fall in urine flow associated with definite though lesser decreases in renal plasma flow glomerular filtration rate and sodium and chloride excretion Ordinarily there was a moderate rise in pulse rate but little or no change in arterial pressure although occasionally the pressure decreased sharply (vaso vagal collapse) During similar experiments patients with diabetes insipidus usually showed only slight decreases in urine flow but did show the normal reduction in renal plasma flow glomerular filtration rate and electrolyte excretion This was true when there were negligible effects on arterial pressure However, when vaso vagal collapse occurred either spontaneously or as a result of the venous congestion, patients with diabetes insipidus exhibited a marked antidiuresis which was accompanied at first by equally marked decreases in renal plasma flow glomerular filtration rate and electrolyte excretion but which persisted with increased inulin U/P ratio for a half to one hour after the arterial pressure and the other renal functions had returned to control values

mus not only the pars nervosa but also the median eminence and the infundibular stem are deprived of their nerve fibers This is important because the last two structures are histologically similar to the pars nervosa or the posterior lobe of the pituitary gland The possibility exists that all three parts are concerned in the elaboration of the anti diuretic principle

Apparently the failure of a number of investigators to produce experimental diabetes insipidus by these procedures was due to two factors The removal of the neural division was not complete or section of the infundibular stem was not high enough in both instances the proximal part of the stem in the median eminence being left intact Also during the operative intervention so much damage was done to the pars anterior that diabetes insipidus did not develop even if the removal of the neural division had been complete The second factor is mentioned in connection with the von Hann[61] theory which holds that diabetes insipidus is caused by the destruction of the supraoptic hypophyseal system only in the presence of sufficient pars anterior to maintain to a certain extent the normal metabolism and activity of the organism

Gersch[53] made an important contribution to the structure and function of the parenchymatous glandular cells in the neuro-hypophysis He described the specific parenchymatous cells of the neuro hypophysis of the rat and distinguished them clearly from neuroglia cells elsewhere in the central nervous system by their characteristic cytoplasmic inclusions The glandular cell was present in all mammalia examined whose glands yielded the antidiuretic substance The distribution of the gland ular elements was strictly limited to the places from which the anti diuretic substance had been extracted It was found that the parenchymatous cells were clearly demonstrated in the rat to extend from the infundibular process through the stalk up to and including the eminentia saccularis Brooks and Gersch[54] have shown also in the rat that these cells are enclosed by neural terminations of the supraoptico hypophyseal system There could hardly be a closer correspondence between the topographical distribution functional cytology and innervation of the parenchymatous glandular cells in the rat s neuro-hypophysis on the one hand and the requirements of the most widely accepted theory of diabetes insipidus The important elements of the dominant theory of the pathological physiology of diabetes insipidus are that the anti diuretic substance is liberated by glandular cells of the neuro-hypophysis

hypothalamico-hypophyseal system but also the secretion of the pressor and oxytocic components These components could not be extracted in appreciable quantities from the hypophysis after injury to the hypothalamico hypophyseal system

It appears that the antidiuretic and pressor responses of the posterior lobe of the pituitary gland are two physiological effects of a single active principle VanDyke[50] also considered the two principles to be identical It is known that the antidiuretic effect is obtained with the pressor principle It has been suggested that the chief function of the latter may be in the regulation of water metabolism Stehle[51] was able to obtain antidiuretic effects with doses of pressor substances which were too minute to give a pressor action, and suggested that the function of the pressor principle may be more concerned with water metabolism than with the vascular system Furthermore, Geiling[5] pointed out that in man therapeutic doses of solution of the pituitary U S P or of pitressin given intramuscularly or subcutaneously, did not give any significant rise of blood pressure in spite of marked pallor He concluded that the pressor component may act as an efficient regulator in the exchange of metabolites between the blood and tissues and exercises a renal function

Ranson and associates[33] have shown that bilateral hypothalamic lesions produced experimental diabetes insipidus in cats and monkeys This disturbance occurred only when the lesions interrupted the supraoptic hypophyseal tracts with resulting atrophy of the neural division of the hypophysis Removal of the neural division or the interruption of the supraoptic hypophyseal tracts as they pass through the median eminence and infundibular stem without injury to the hypothalamus leads to the production of diabetes insipidus

These authors have emphasized that the supraoptic hypophyseal system forms an anatomical and functional unit and that injury to any part of it is reflected by the presence of degenerative changes in the other parts From this point of view removal of the neural lobe was equivalent to interruption of the supraoptico-hypophyseal tract in the hypothalamus in the sense that in both instances that organism is deprived of antidiuretic hormone Likewise section of the infundibular stem was equivalent to such interruption with the difference that in the former the nerve fibers are cut after they have collected together in the stem while in the latter they are separated from their cell bodies as they pass medially to enter the median eminence There is one difference between these two procedures When the tracts are interrupted in the hypothala

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and that their activity is regulated by the supraoptico-hypophyseal system

These deductions explain practically all the apparently conflicting results which are said to follow interference with the nerve supply of the neuro hypophysis at its origin or in its course or ablation of the infundibular process They also explain the loss in activity of the denervated gland In the adult the cytological changes in these cells coincided with physiological fluctuations in the rate of secretion of the antidiuretic substance into the blood stream These coincidences were too striking to be regarded merely as accidental and are proof that the parenchymatous glandular elements of the neuro-hypophysis produce and secrete the antidiuretic substance

The site of formation of the posterior lobe hormone had been a matter of controversy Either the pars nervosa or the pars intermedia of the hypophysis was thought to be the site of elaboration of the pressor antidiuretic and oxytocic principles Some considered the pars intermedia because it was felt that an organ of purely nervous origin such as the pars nervosa could not have an endocrine function The pars tuberalis and the tuber cinereum have been considered also However Gersch's work explains why various areas do have certain secretory function of the antidiuretic substance Contrary to views which have been presented previously, there is now good evidence to suggest that the pars neuralis is an important gland of internal secretion

Furthermore Geiling and his coworker[55] presented evidence that the pars nervosa was entirely independent of the pars intermedia and elaborated the physiological active components of the posterior pituitary Ranson and associates[33] were impressed with the fact that the degenerative changes following interruption of the supraoptico hypophyseal tract appeared to be confined to the neural division The pars intermedia was histologically intact although the neural division showed degenerative changes and was almost entirely lacking in the antidiuretic activity In order to test whether the histological normal pars intermedia was functioning normally they assayed these glands for their melanophore expanding activity which is the accepted method for testing its normal function The pars intermedia of these glands was found to be physiologically active as well as histologically intact

There has been positive evidence of the hormonal nature of diabetes insipidus This was corroborated particularly by Verney and associates[11] who used heart-lung kidney preparations Starling and Verney[12] per

fused the kidney by means of a heart lung preparation and observed that the isolated kidneys developed a marked polyuria the urine formed being dilute and the concentration of chlorides low The addition of pituitary hormone to the perfusing blood restored to normal the urine flow and composition They suggested that substances having an action similar to that of pituitary hormone regulated the output of water and chloride in the intact animal and that the absence from the blood stream of such substances was thought to be the essential cause of the diuresis after drinking water of the polyuria of isolated perfused kidneys of the dog and of the polyuria of diabetes insipidus In addition Verney[a] determined the effect on urine excretion of switching various parts of tissues of another dog into perfusion parallel with the kidney of the heart lung kidney preparation There occurred a marked inhibition of the diuresis and an increase in the chloride concentration when the head and neck of a dog were perfused in a series with the kidney The heart lung kidney preparation apparently picked up something from the head of the dog which was indistinguishable in its effects from pituitrin Perfusion of the hind limbs of a dog in series with the kidney had no effect on the diuresis When the hypophysis was extirpated from the head of the dog which was in perfusion parallel with the heart lung kidney preparation the polyuria normally seen in the latter returned When one kidney was denervated post pituitary extract inhibited an induced water diuresis to the same degree on the two sides the responses maintained a close parallelism

In other words there are two conditions under which profuse watery diuresis is observed These are perfusion of the dog s kidney in the isolated state and the ingestion of a large volume of water by the normal mammal The diuresis seen in the perfused isolated kidney is specifically inhibited by the addition of posterior pituitary extract to the perfusing blood The fall in the output of water was accompanied by an increase in the concentration of chloride in the urine and the rate of chloride excretion These effects of posterior pituitary extract are closely simulated by switching the head of a dog to perfusion parallel with the kidney The inhibition of diuresis and increased secretion of chloride depended on the presence of the pituitary in the perfused head There can be little doubt about the correctness of the views advanced that the profuse watery diuresis exhibited by the perfused isolated kidney is due to the divorce of the kidney from the inhibitory influence of the

posterior pituitary antidiuretic substance and has essentially the same etiology as diabetes insipidus

Recently Verney[5, 6] made some unique and extensive observations on the absorption and excretion of water and the antidiuretic hormone and on the profuse watery diuresis following water ingestion and described them in an 81-page article[5]. The importance of these investigations resulted in the possibility of determining whether the posterior pituitary antidiuretic substance was being secreted continually according to the contemporary osmotic pressure of the arterial plasma and being as continually and reversibly engaged in determining the rates of water and chloride excretion by the kidney. The response to sodium chloride was shown to be osmotically determined, and he therefore introduced the term "osmoreceptors" as descriptive of the autonomic receptive elements with which the neurohypophysis is linked functionally and through whose activation the pituitary antidiuretic substance was shown to be released.

According to Verney the hypothesis that water diuresis is conditioned by an inhibition of secretion of antidiuretic substance by the neurohypophysis implies a prior governance of this secretion by the osmotic pressure of the arterial plasma. Therefore he determined the effects of a rise in the osmotic pressure of the carotid plasma on the secretion of the kidneys during water diuresis in dogs. It was first necessary to see whether intracarotid injection of isotonic solutions at different temperatures and intravenous injections of hypertonic solutions produced any effect on the course of urine flow. They were found not to do so. When however hypertonic solutions were injected into the carotid, definite inhibitory responses were observed.

The shape of these responses suggested that they were of pituitary origin. This hypothesis was put to the test of experiment by measuring the responses to a given injection before and after removal of the posterior lobe. The response to 21 c c of 2 50 per cent NaCL injected into the right carotid in 20 seconds equated closely with the response to 1 0 mU of postpituitary extract injected intravenously, whereas the response to the same intracarotid injection after removal of the posterior lobe was reduced 90 per cent. Then they inquired whether it was indeed the increase in the osmotic pressure of the plasma which was operative in eliciting the response to intracarotid injection and to this end comparison was made of the effects of isosmotic solutions of NaCL and dextrose. The responses were indistinguishable. Verney injected hyper

tonic solutions of sodium chloride and sucrose into the carotid artery and produced quantitatively with both the same release of post pituitary antidiuretic substance The response therefore was due not specifically to NaCL but to the rise in osmotic pressure The osmotic determination of the phenomenon he considered now to be beyond cavil

The osmoreceptors wherever they may be do not accommodate during short period exposure to a rise in the osmotic pressure of the carotid plasma produced by NaCL Doubling the period of exposure to the same rise caused the release of at least double the quantity of antidiuretic substance This lack of accommodation would be expected on the basis of view that the osmoreceptors are continually engaged in controlling the antidiuretic function of the pituitary

When an infusion of NaCl was made into the carotid artery over a period of 10 minutes the urine flow was inhibited earlier than when the same infusion was made into the malleolar vein and as the strength of the infused solution was reduced this difference became greater The cause of the earlier onset of the inhibition when the infusion was made into the carotid artery must be attributed to the increase in osmotic pressure of the blood in the vascular bed supplied by the carotid over and above that of the aortic blood

The recovery of urine flow when the intracarotid infusion is stopped shows that the secretion of pituitary antidiuretic substance is being inhibited by a fall in blood chloride and consequent depression of activity in the osmoreceptors The progression of this recovery is to be attributed to the gradual destruction in the kidney and perhaps in the blood of the quantity of antidiuretic substance which was maintaining the secretion of urine at a non diuretic level Water diuresis then may be described as a condition of physiological diabetes insipidus there can be little doubt that the antidiuretic secretion of the neurohypophysis is a hormone in the physiological sense its liberation being continuously governed by the contemporary concentration of chloride and possibly of other osmotically active substances in the arterial plasma

The presence of osmoreceptors connected by nerve paths with the pituitary was postulated by Klisiecki and associates[58] Verney[5] then determined the site of the osmoreceptors believing they lie in the vascular bed e g the supraoptic nucleus supplied by the internal carotid artery He found that the antidiuretic response to an intracarotid injection of a hypertonic solution of NaCl vanished as the result of ligation of the internal carotid artery He concluded therefore that the receptors lie in the vascular bed normally supplied by the internal carotid

posterior pituitary antidiuretic substance and has essentially the same etiology as diabetes insipidus

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diuretic substance is secreted by the posterior pituitary (2) this substance is a true hormone passes into circulation and acts on the kidney, (3) the pituitary hormone in its circulation through the kidney filters through the glomerulus and escapes into the urine in which it is relatively stable and easily detectable, (4) the need for water conservation by the body is a stimulus for the secretion of this hormone

Shannon[60] carried this problem further and determined the rate of liberation of the antidiuretic hormone by means of constant pituitrin infusion in dogs with diabetes insipidus and in normal dogs Graded antidiuresis in the animal with diabetes insipidus when normally dehydrated was obtained only in the range of 1 0 to 5 0 milliunits (pressor) per hour This range of hormone administration was found also to be physiologically active in the normal animals These observations together with others place the normal rate of liberation of the antidiuretic hormone in a 10 to 15 kilo dog in the order of magnitude of 1 0 to 5 0 milliunits per hour

Verney too determined the rate at which the antidiuretic substance was being secreted continuously in the nonhydrated dog and obtained a figure which agreed well with that of Shannon

Anterior Pituitary — There is the function of another part of the pituitary gland that is the pars glandularis or the anterior pituitary gland which is necessary for the development of diabetes insipidus In general it has been found difficult to produce diabetes insipidus after complete removal of the whole pituitary gland If the anterior pituitary gland is left intact the suppression of secretion of the posterior lobe readily causes diabetes insipidus Furthermore if diabetes insipidus has been produced experimentally it may be abolished by the removal of the anterior pituitary gland Von Hann[61] apparently was the first to call attention to the importance of the pars anterior in diabetes insipidus According to her theory the failure of total hypophysectomy to produce polyuria is due to the secretion by the anterior lobe of a hormone which antagonizes the posterior pituitary antidiuretic hormone to the production of a diuretic principle by the anterior pituitary gland Her view was based on the post mortem records of 20 subjects with lesions involving the posterior lobe In 9 cases which did not have diabetes insipidus no functioning anterior lobe tissues were present On the other hand the only ones with diabetes insipidus were those with viable anterior lobe tissue and destruction of the posterior lobe Hirsch[61] did not believe her theory because he observed a patient with diabetes insipidus that showed at autopsy a tumor which destroyed the entire pituitary gland

artery This is interesting because one of our cases of diabetes insipidus showed calcification of the internal carotid artery by x ray

Evidence for the true hormonal nature of the antidiuretic principle has been presented When account is taken of the exactness with which the degree of hydration is maintained, it seems likely that the relationship between the pituitary gland and kidney must be readily adjustable and therefore probably under hormonic control This assumption presupposes that the body requirements for water absorption in the kidney will to a large measure determine the degree of hypophyseal activity in the production of the antidiuretic hormone

Proof of this idea has been presented by Gilman and Goodman[59] The relative stability of pituitary extracts in urine suggested to them that the antidiuretic hormone might be demonstrated in this body fluid whenever it was necessary for the organism to conserve water Under such conditions the blood concentration of the hormone might rise to levels exceeding the renal threshold thus permitting the substance to pass into the urine This physiological need for the conservation of water was produced in rats that were dehydrated by either water and food withdrawal or by the oral administration of sodium chloride Suitably concentrated and dialyzed urines from these animals showed on bio-assay marked antidiuretic activity Control animals given water ad libitum showed no urinary excretion of the antidiuretic hormone Experiments were conducted also on hypophysectomized animals This group of animals from 7 to 14 days after operation was deprived of all water during the period of urine collection and normal control animals were dehydrated at the same time under identical experimental conditions The volume of urine from the hypophysectomized group of rats was approximately three times greater than that from the controls It is evident therefore that the experimental animals were more dehydrated than the control group and had a greater stimulus for water conservation Despite this need however assay demonstrated that the urine of the hypophysectomized rats contained no antidiuretic substance while the control urine exhibited unmistakable antidiuretic activity Thus it would appear that the pituitary gland is definitely the source of the antidiuretic substance in the urine

Further proof of the hypophyseal origin of the antidiuretic principle of the urine was obtained by the demonstration of a similarity between the chemical properties of pharmacological preparations from the gland and the urinary principle The results offered definite evidence for the hormonal role of the antidiuretic principle as follows (1) an anti

attempts to link up the effect of some glands of internal secretion with the polyuria and polydipsia of diabetes insipidus However in general these effects on polyuria and polydipsia are only secondary to those of the posterior lobe of the pituitary gland and its allied structures

Thyroid and Thyroidectomy in Diabetes Insipidus

The thyroid gland was among the earliest to be discussed concerning its effect on water balance Considerable progress has been made in our knowledge of the physiology of the thyroid gland in relation to other organs of internal and external secretion A definite relation has been found to exist between the thyroid and the pituitary gland and the excretion of water through the kidneys

Investigators have reported that removal or disease of the thyroid gland causes an alteration in the pituitary body[68 69 70 71] As early as 1889 Rogowitsch[3] found an increase in certain elements in the glandular or anterior part of the pituitary glands in thyroidectomized dogs and rabbits In 1908 Herring observed after thyroidectomy an increased activity of cells in the pars intermedia and most striking changes in the nervous part of the posterior lobe and in the laminae forming the floor of the third ventricle

More recently investigators have reported that thyroidectomy in experimental diabetes insipidus decreases or abolishes the polydipsia and polyuria and that the subsequent administration of desiccated thyroid reestablishes the syndrome[73 74 75 76 77] A similar effect was noted also after thyroparathyroidectomy and subsequent administration of thyroid extract in dogs[73] Strauss[78] reported a 9 year old boy with diabetes insipidus which progressively disappeared with the gradual onset of myxedema at the age of 13

These experimental results were confirmed[9] in human diabetes insipidus due to postencephalitic Parkinson s disease In two of our patients the polyuria and polydipsia were relieved by total thyroidectomy and reestablished by the administration of thyroid extract A third patient with diabetes insipidus of idiopathic origin was not improved by total thyroidectomy However in this case it was believed that the patient had accessory thyroid tissue present because her basal metabolism blood cholesterol and the iodine in the blood and urine were much the same before and after the operation In addition there were no signs of myxedema Before thyroidectomy in the first two cases the fluid

except for a microscopic remnant of the anterior lobe Nevertheless von Hann s observation has been corroborated by those[6] who have produced experimentally permanent polyuria by simple extirpation of the posterior lobe of the pituitary gland The experimental results of Richter[37] were in agreement with these findings Total hypophysectomy in rats was not followed by permanent diabetes insipidus, whereas this condition was produced by removal of the posterior lobe alone This theory suggests that the excretion of water by the kidney is normally governed by a balance of the activities of the anterior and posterior lobes This balance may be disturbed by removal of the latter, by interruptions of its nerve connections with the hypothalamus or by the injection of an anterior lobe extract after total hypophysectomy Keller[63] suggested that the diuretic action of the anterior lobe was brought about through its thyrotropic hormone When the anterior lobe extract was administered daily to a hypophysectomized animal, the water intake did not show any increase until the lapse of 24 to 48 hours It then increased progressively for 12 days and from then on gradually declined to the normal level although the injections were continued The delay in onset and the gradual development of the polydipsia, together with the apparent refractoriness of the animal to continued treatment suggested very strongly the action of the thyrotropic principle[61] In other words diabetes insipidus cannot occur or be produced unless there is a functioning anterior lobe tissue present Richter and Wislocki[65] also presented evidence that the pars anterior tissue had to be present before posterior lobe removal resulted in an increased fluid output

There is further evidence that the anterior lobe has a diuretic principle and that its extract produces polyuria This was first pointed out by Teel and Cushing[66] and by others[67] They noted a marked increase in the water intake and output in dogs which lasted for 1 to weeks after the injection of an extract of the fresh anterior pituitary lobe In these dogs the diuresis followed polydipsia which they considered to be primary The growth hormone was also present in this extract

It appears that a normal water balance is dependent on a balance between the diuretic property of the anterior lobe and the antidiuretic activity of the posterior lobe of the pituitary

Harris[6] recently presented a 40 page review of the neural control of the pituitary gland This analysis is concerned particularly with evidence relating to various aspects of neural excitation and control of both the neurohypophysis and adenohypophysis

With progress in recent years in endocrinology there have been

attempts to link up the effect of some glands of internal secretion with the polyuria and polydipsia of diabetes insipidus However in general these effects on polyuria and polydipsia are only secondary to those of the posterior lobe of the pituitary gland and its allied structures

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intake and output were approximately 10 liters and the basal metabolism was normal. During the postoperative course the daily fluid intake and output dropped so that in a month these values were about 3 to 3½ liters. The basal metabolism decreased to a level of about minus 23 per cent and the blood cholesterol increased. The thyroid glands in two cases showed some evidence of hyperactivity on microscopic examination.

The effect of the oral administration of thyroid extract on the water balance of these patients after thyroidectomy was studied in two cases. The results in one of these cases are illustrated in Fig 2. Shortly after thyroid was administered the polyuria and the polydipsia reappeared and persisted for an appreciable period of time after the omission of the thyroid extract.

Whether the effect of thyroid on water excretion is due to an increased basal metabolism, or whether it is due to some other mechanism was studied in two of the thyroidectomized patients by giving them dinitrophenol until the metabolism was elevated. Subsequently, thyroid was given for a comparison of the intake and output of fluid during these periods.

The comparative results of the effect of dinitrophenol and thyroid are shown in Fig 3. The administration of dinitrophenol did not appear to produce any great change in the water balance even though there was a prompt and great increase in the metabolic rate. The subsequent intake of thyroid did not cause as great an increase in the intake and output of fluid as it did when it was given without the previous administration of dinitrophenol. The comparative results with dinitrophenol and thyroid suggest that the diuretic action is not explained by an increased metabolic rate but probably is due to some specific mechanism.

The removal of the thyroid gland was shown to have an effect on the anterior lobe of the pituitary gland by the finding of positive evidence of the excretion of thyrotropic hormone in a case after thyroidectomy.

There appears to be an imbalance in the thyroid pituitary relationship in diabetes insipidus which may play a part in the clinical aspects of the disease. This disturbance may be specific and due not only to the ability of the thyroid to raise the basal metabolism but also to an active diuretic principle of this gland.

The hyperactivity of the thyroid gland may be due to stimulation resulting from increased activity of the anterior lobe of the pituitary gland in diabetes insipidus and indicates that the diuretic effect of the anterior lobe of the pituitary gland is through its regulation of the

Fig 2 Effect of total thyroidectomy and of the subsequent intake of thyroid on the intake and output of fluid 0.39 gm of thyroid was taken daily for the first nine days and 0.52 gm for the last six days

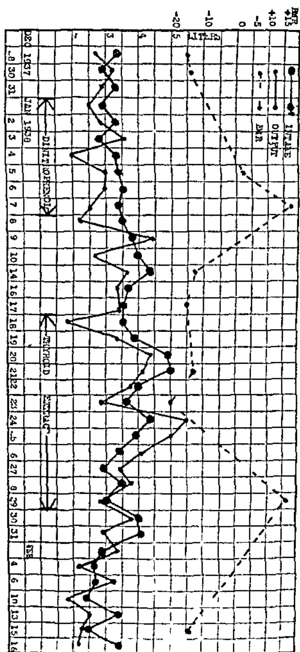


Fig 3 Comparative effects of dinitrophenol and subsequently of thyroid on the intake and output of fluid one and one half years after total thyroidectomy o   gm of dinitrophenol was given daily for the first four days then o 3 gm daily Thyroid was given daily in doses of o 13 gm for four days o 2 gm for three days and o 4 gm for five days

thyroid This is suggested also by the animal experiments in which diuresis produced by the injection of solutions of the anterior lobe of the pituitary gland is abolished by thyroidectomy

Other Endocrine Glands

The ovaries testes adrenal and parathyroid glands have been reported to have an effect on this disease The relation of the effect of the female hormones is discussed under Ammotin Antuitrin S and *Pregnancy in Diabetes Insipidus* *In the cases which I have observed* female sex hormones had no appreciable effect on the symptoms of diabetes insipidus In none of these patients did diabetes insipidus develop following menopause or removal of the ovaries nor has there been any improvement in diabetes insipidus following the administration of ovarian extracts However pregnancy may effect the polyuria and polydipsia of this disease Del Castillo and Pasqualini[80] described a patient who suffered from diabetes insipidus since the age of 18 years and had a bilateral ovariectomy at the age of 36 years with no effect on the polyuria Estradiol benzoate administration in a week had no effect on the polyuria Accordingly they considered that the diabetes insipidus had nothing to do with pregnancy and castration and could not be influenced by the feminine sexual hormones

In connection with the male sex glands there may be some relation between their function and the polyuria of diabetes insipidus Allen and Stokes[1] reported a cure for diabetes insipidus coincident with bilateral correction of abdominal cryptorchidism in a boy following injection of antuitrin S I saw no improvement in the symptoms of diabetes insipidus in any of the males following injection of testosterone propionate or antuitrin S whether or not there was any evidence of genital dystrophy

Ranson and associates[23] castrated 4 cats with diabetes insipidus and found no significant decrease in the fluid exchange Yet Schlotthauer[illegible] reported that castration alleviated the diabetes insipidus of a 1 year old bull On a theoretical basis the reported fact that the administration of gonadal hormones may suppress the polyuria and polydipsia of this disorder might lead one to expect an increase in fluid exchange rather than a decrease after gonadectomy This hypothesis is interesting because in a group of convicts who had been castrated Hamilton[illegible]

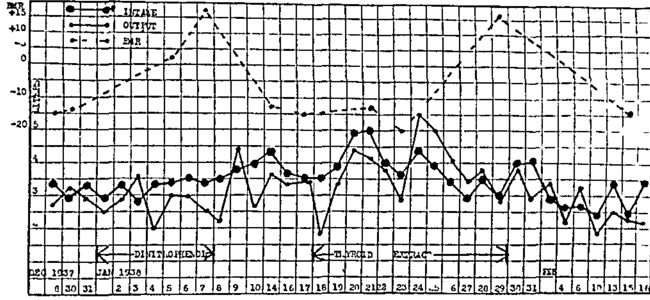


Fig. 5 Comparative effects of dinitrophenol and subsequently of thyroid on the intake and output of fluid one and one half years after total thyroidectomy 0.2 gm of dinitrophenol was given daily for the first four days then 0.3 gm daily Thyroid was given daily in doses of 0.13 gm for four days 0.2 gm for three days and 0.4 gm for five days

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obtained the impression that these eunuchs had a urine volume which was greater than that in non-castrated men housed in the same institution Gottlieb[4] reported that 11 of the 58 cases of adiposo genital dystrophy analyzed by him showed diabetes insipidus so that it was clear that this disorder can occur in the presence of genital atrophy I believe that the association of adiposo-genital dystrophy and diabetes insipidus is coincidental and that this dystrophy is not due to the diabetes insipidus per se Rather it results from certain lesions which cause diabetes insipidus and which if sufficiently extensive to involve the infundibulum may produce adiposo-genital dystrophy

Successful treatment with testicular extracts has been reported Lickint raised the question as to whether diabetes insipidus might not be a genito hypophyseal disease in some cases at least rather than a purely hypophyseal one He obtained with testicular extracts successful results in a case of diabetes insipidus Similar findings have come from Rothmann[86] and Kurumlistis[87] In view of present knowledge it may be reasonable to assume that increased testicular secretion may cause inhibition of the anterior part of the pituitary gland and a resulting amelioration of diabetes insipidus

There has been evidence suggesting a relationship between the adrenal gland and polyuria Ingram and Winter[88] showed that adrenalectomy in cats with diabetes insipidus was followed by a decline in the polyuria although the urine volume did not always fall to normal A syndrome resembling diabetes insipidus may be produced in dogs[89] during daily administration of desoxycorticosterone acetate Britton and his coworkers[90] and Mulinos and associates[91] have developed the hypothesis that the adrenocortical hormone and the posterior lobe antidiuretic hormone are physiological antagonists in relation to certain phases of renal function According to this view diabetes insipidus may be explained by the unmasking of the diuretic effect of the adrenal cortex when there is a deficiency of posterior lobe secretion

Winter and Ingram[9] determined the effect of injections of cortico-adrenal extract and of desoxycorticosterone acetate on animals with experimental diabetes insipidus and in normal animals The daily injection of desoxycorticosterone acetate markedly increased the severity of diabetes insipidus when it was present Normal dogs receiving such injections developed a syndrome which resembled a very mild diabetes insipidus Pitressin only partially controlled desoxycorticosterone poly

uria even if given in dosage several times that required to render a dog with diabetes insipidus non-polyuric. Creatinine clearance studies showed that both in normal dogs and those with diabetes insipidus desoxycorticosterone acetate reduced tubular reabsorption of water. In contrast to the results in dogs, injections of desoxycorticosterone acetate failed to increase the daily water exchange in normal cats. There have been discussions for and against the hypothesis that the adrenocortical hormone and the posterior lobe antidiuretic hormone are physiological antagonists.

The polyuria produced by desoxycorticosterone acetate injections is mild compared with true diabetes insipidus. The finding that desoxycorticosterone injections retarded tubular reabsorption of water in dogs does not prove that the adrenal cortex is responsible for the similar phenomenon seen in diabetes insipidus. It merely may be an interesting pharmacodynamic effect of the hormone. Although not proven, the hypothesis of the participation of the adrenal cortex in the establishment of the polyuria of diabetes insipidus has some interesting features.

While animal experimentation has demonstrated the antagonistic effect of the adrenal cortical hormone to the antidiuretic principle from the posterior lobe of the hypophysis, no such interrelationship has been shown to exist in the human subject. However, it is worthy of note that Bartsolas (463) described an unusual case of adrenal virilism with cortical tumor and diabetes insipidus in a 8 month old girl with a daily urine volume of 4000 cc. Anderson and Murlin[9] determined whether or not the already existing polyuria of human diabetes insipidus would be aggravated by adrenal cortical extract in a 19 year old boy with severe diabetes insipidus of undetermined etiology. They described the effect of adrenal cortical extract and pitressin on the water and electrolyte exchange in this patient. These authors confirmed the physiologically antagonistic action of adrenal cortical extract and pitressin on the excretion of sodium chloride and water in the human subject with diabetes insipidus. Adrenal cortical extract was unable to produce an increased excretion of potassium unless pitressin was supplied. They suggested that facultative reabsorption of water as induced by pitressin must be in progress before the kidney tubule can selectively excrete sodium and potassium ions.

The parathyroid glands, too, may influence water excretion under certain conditions. Shelling[1] described how the injection of the hormone of this gland may produce diuresis within a few hours. How-

ever, the parathyroid glands in two of our cases were normal histologically

The liver has been recognized to bear some relation to water metabolism In experimental liver damage and liver disease in man water retention has been noted The presence of antidiuretic substances in urine has been associated with liver dysfunction It has been suggested that this may be the neurohypophyseal antidiuretic hormone appearing in the urine because it is not inactivated effectively by the damaged liver (464) To test the role of the liver in the inactivation of posterior pituitary antidiuretic hormone Eversole and associates (465) studied the response of animals to pitressin administered through an hepatic portal drainage as compared with the response of those which received the hormone by other routes They found that when pitressin was injected into a site with hepatic portal drainage it was less effective than when introduced into the general circulation These results were interpreted by the theory that the liver is one site of inactivation of circulating posterior pituitary antidiuretic hormone

Also there have been other papers[9] showing the relation of certain neurogenic and endocrine factors to water metabolism

Summary of Physiology

Diabetes insipidus is a hormonal disease primarily due to a deficiency in secretion of the antidiuretic principle of the posterior lobe or the neural division of the pituitary gland The secretion of the antidiuretic hormone is governed by the supraoptic-hypophyseal tract Injury to this tract results in a marked diminution or abolition of the antidiuretic hormone with subsequent diabetes insipidus The lack of antidiuretic hormone causes a deficiency in the reabsorption of water by the loop of Henle in the kidneys with consequent polyuria This is corrected by the administration of pituitary extract Thirst appears to be secondary to the loss of water and is activated by a mechanism in the brain probably in the hypothalamus The effect of other glands of internal secretion on polyuria and polydipsia appears of secondary importance

The normal water balance is dependent on a balance between the diuretic activity of the anterior lobe and the antidiuretic activity of the posterior lobe of the pituitary gland Diabetes insipidus apparently cannot occur unless there is functioning anterior lobe tissue present

Pathology

Introduction

The pathology of diabetes insipidus is an unusually interesting subject because of the great variety of lesions which may produce the disease. It is difficult in certain respects to classify diabetes insipidus because of its varied origin.

The pathology centers around the pituitary gland and its associated structures. Why the pituitary gland becomes diseased or ceases to function is a question. This is clear when there is present any one of the many obvious pathological conditions which affect the pituitary gland or its surrounding structures. The idiopathic cases of diabetes insipidus have presented in the past the greatest mystery. The pathology of the idiopathic cases had not been known definitely because apparently such actual cases with detailed autopsies had not been reported. However in light of our newer experimental knowledge of diabetes insipidus and in view of pathological reports of cases presented here the mystery becomes unfolded. The pathology as presented here I believe fits in with modern experimental observations particularly with those of Ranson and associates[33]. These authors have made a great contribution to the physiology and pathology of the disease and have brought to the fore the basic lesions involved. Actually it appears that the so called idiopathic cases are not idiopathic but are due to an organic lesion which produces degeneration of the supraoptic hypophyseal system.

In contrast to the so called idiopathic cases there are an appreciable number of post mortem examinations on cases of diabetes insipidus known clinically to be due to a variety of lesions. Unfortunately the cases with thorough histological studies of the hypophysis and hypothalamus are so few that it is difficult to evaluate them. Stremler[36] in a critical analysis of the literature found that isolated lesions of the hypothalamus or the hypophysis can result in diabetes insipidus. Evidently few observers had detected the secondary hypercellularity and atrophy of the neural division after hypothalamic lesion or the secondary atrophy of the supraoptic nuclei which might be expected to accompany those cases in which the neural division was destroyed by various processes. It is likely that unless a search was made specifically for these changes they would escape notice. It has been reported in some cases that hypothalamic lesions or destruction of the posterior lobe failed to bring about

diabetes insipidus but this should not be considered too seriously. Some of the fibers of the supraoptic hypophyseal tract may have escaped interruption. Significant portions of the infundibular stem or median eminence may have been left intact, or the pars anterior may have suffered severe damage.

In 1913 Cushing gave a lecture before the Massachusetts Medical Society on diabetes insipidus, a disease encountered often with tumors of the pituitary gland. This was the theme of Cushing in the early days. Some of his friends suggested that he had become too pituitary minded and that he was inclined to attribute every exotic new clinical entity to pituitary malfunction[9]. Actually he was not far from wrong about diabetes insipidus. He was disturbed a few years later when his associates Bailey and Bremer[11] discovered that diabetes insipidus could be induced in animals by making small lesions at the base of the brain that did not encroach on the pituitary. Cushing had believed that the condition resulted from injury to the posterior part of the pituitary gland. It turned out that both theories were right because the area at the base of the brain which Bailey and Bremer had injured, contains nerve cells that control the secretory cells in the posterior pituitary gland. However Frank[16] was credited with being the first to call attention to the relation of the pituitary gland to diabetes insipidus because he presented in 1910 a case of diabetes insipidus caused by a bullet lodged in the sella turcica.

In Berblinger's[98] case the posterior lobe and the infundibulum were infiltrated with sarcomatous material and the anterior lobe was not involved. Metastatic carcinoma to the posterior lobe as the cause of diabetes insipidus was reported by Von Gierke[99] and by Sekiguchi[100]. Marañon[101] described [illegible] cases in which the pathology in the nature of sclerosis, atrophy and hemorrhage was confined to the pars nervosa. A case with lymphogranuloma at the base of the brain with destruction of the posterior lobe was presented by Takao[10]. Zadek[30] had two cases in which the posterior lobe was destroyed, but the hypothalamus was intact as well as the pars anterior.

It is evident from the literature that posterior lobe destruction can cause diabetes insipidus. Obviously in earlier reports investigators did not refer to atrophy of supraoptic nuclei because at that time the supraoptic-hypophyseal system was not generally recognized. In a number of publications Ranson and associates have presented a mass of experimental evidence which clearly shows how destruction of the various parts of the supraoptic component of the hypothalamico hypophyseal

system was related to diabetes insipidus About half of the fibers of the supraoptic hypophyseal tract must be interrupted or the neural division must be removed nearly completely before polyuria and polydipsia become demonstrable Apparently the supraoptic nuclei are the only hypothalamic nuclei the destruction or atrophy of which may be responsible for this disorder

The earliest authors to suggest that diabetes insipidus could result from destruction of the different parts of the supraoptic hypophyseal system were Kary[103] Pines[104] and Greving[1] Kiyono[106] gave an interesting post mortem report on a case of diabetes insipidus of 13 years duration which showed degenerative changes in the supraoptic and filiform nuclei with marked atrophy of the posterior lobe Futcher[1] and DeSanto[108] indicated too the possibility of the involvement of the supraoptic hypophyseal system in diabetes insipidus Biggart[10] presented three cases in which the lesions were in a position to destroy the supraoptico-hypophyseal fibers Two of these cases were due to brain tumor and one to encephalitis

In recent years there have been numerous reports on the atrophy of the posterior lobe of the pituitary in cases of diabetes insipidus in which the primary pathological lesion was in the hypothalamus[110] The status of the anterior lobe of the pituitary gland is important in the pathology of diabetes insipidus Some functioning anterior lobe tissue must be present for the disease to develop Von Hann[61] first drew attention to such cases in which the posterior lobe was involved In eleven of these the pars anterior was said to be unchanged In nine there was complete destruction of the hypophysis without the development of diabetes insipidus It was concluded that the pars anterior must be at least partially intact if destruction of the posterior lobe is to result in diabetes insipidus because the pars anterior probably secretes a diuretic substance which is antagonistic to the posterior lobe antidiuretic substance

It is evident from experimental data and the literature that the fundamental pathological finding in diabetes insipidus is the degeneration or destruction of the supraoptic hypophyseal system which regulates water balance in the presence of normally functioning anterior lobe tissue

Statistical Data

Fink[1] made a critical analysis of 107 necropsies of diabetes insipidus reported in the literature from 1868 to 19 7 He found that sixty eight

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Statistical Data

Fink[111] made a critical analysis of 107 necropsies of diabetes insipidus reported in the literature from 1868 to 19 7 He found that sixty eight

patients or 63 per cent, had tumors about the base of the brain or the posterior cranial fossa Fourteen cases or 13 per cent, were due to syphilitic processes either basal meningitis or gummas in or near the hypophysis In five cases the lesion was a tuberculoma or tuberculous meningitis of the base while nine cases were due to non syphilitic inflammatory conditions in the same location The remainder were included under traumatic injuries In most instances the tumors were not of localizing value since they involved more than one structure at the base of the brain There were ten cases of a gumma or caseous tubercle and fifteen instances of a discrete metastatic carcinoma nodule limited to the posterior lobe of the hypophysis or infundibulum

The pathological lesions held responsible for diabetes insipidus were of three types depending on the prevailing theories of the experimental production of polyuria The first period was influenced by Claude Bernard[11], who in a classic experiment demonstrated that puncture of the corpus restiforme in the floor of the fourth ventricle was followed by polyuria The second period may be termed the hypophyseal period which originated after Frank[20] and drew attention to the association of diabetes insipidus with signs of a hypophyseal lesion The third period is based on experimental physiology It originated in the work of Camus and Roussy[113] who showed that injury to the floor of the third ventricle near the insertion of the infundibulum led to polyuria Now we might say that there is a fourth period based on the work of Ranson and others which shows that *the supraoptic hypophyseal system is fundamentally* involved in the pathology of diabetes insipidus This last theory has influenced our present day conception of the disease

Author's 112 Cases of Diabetes Insipidus — The underlying pathology in our 112 cases of diabetes insipidus has presented a most interesting variety of etiological factors as to the cause of the diabetes insipidus (see Table I)

An analysis of these cases shows that the idiopathic cases had the highest incidence occurring in fifty patients or 45 per cent Brain tumors had the second highest frequency appearing in thirty six patients or 32 per cent Syphilis was the important etiological factor in seven cases or 6 per cent Congenital syphilis was present in another instance but was not the underlying cause since this patient had two brain tumors

Other etiological factors appeared with less frequency as follows post encephalitis heredity xanthomatosis leukemia chorea fractured skull calcification of internal carotid artery, basal arachnoiditis cerebral

TABLE I

PATHOLOGY OF 112 CASES OF DIABETES INSIPIDUS

	No of Cases
Idiopathic (? hysterical 3 ? trauma 6)	50
Brain tumor	36
Syphilis	7
Heredity	3
Post encephalitic	3
Xanthomatosis	2
Myeloid leukemia	2
Chorea	2
Lymphoma	1
Fractured skull	1
Cerebral arteriosclerosis	1
Birth injury	1
Calcified internal carotid artery	1
Post vaccinal	1
Basal arachnoiditis	1
Total	112

arteriosclerosis lymphoma post vaccinal encephalitis and questionable birth injury

Idiopathic Diabetes Insipidus

Diabetes insipidus of idiopathic origin constitutes the largest group of the cases that I have observed in the past twenty years In our study 45 per cent of 112 cases of diabetes insipidus were of idiopathic origin without any clinical abnormalities or manifestations of this disease except for polyuria and polydipsia Because of the great importance of autopsy on such cases the following two autopsies are presented The first case which finally came to autopsy is one I observed for 20 years with many studies I believe it is the most thoroughly studied case on record from clinical and pathological views It is presented in considerable detail because it fits in with the modern theories of diabetes insipidus

Case 1—This patient was a single 41 year old house painter who was born in Boston His diabetes insipidus began in 19 4 He noted one afternoon while working on his automobile that suddenly he had to pass a large amount of urine and that shortly thereafter he had polydipsia These symptoms persisted the rest of his life His daily fluid intake and output usually ranged from 8 to 11 liters

In the past he had had measles mumps scarlet fever and influenza all some time before diabetes insipidus appeared There was no history of rheumatic fever or encephalitis There had been no history of headaches no trouble with his eyes no blurred or double vision The history of his ears nose throat mouth and cardiorespiratory system had all been negative He had a duodenal ulcer for many years which occurred subsequently to diabetes insipidus The ulcer was controlled with diet and alkalies He drank large amounts of alcohol over long periods of time and had many alcoholic bouts The genitourinary history aside from the polyuria had been negative

His best weight was 140 pounds near the onset of the disease and then varied from 125 to 135 pounds The family history was irrelevant

The physical examination through the years showed the patient to be well developed and slightly under nourished His height was 5 ft 7½ inches and weight was as already stated His blood pressure was 110/80 Thorough neurological and physical examinations were normal However the heart showed a slight systolic murmur at the apex which was variable Spinal fluid was under normal pressure and chemical analyses of it were normal X rays of the skull chest and other bones were normal Electro encephalograms and pneumoencephalograms were normal

Treatment—He had been on various forms of pituitary therapy with complete control of the polyuria and polydipsia Pituitrin intranasally and subcutaneously gave relief Pitressin tannate in oil gave complete relief of the polyuria and polydipsia

LABORATORY DATA

	Without Pituitrin	*With Pituitrin*
Basal metabolism	−16%	−17%
Hematocrit Readings		
Corpuscles	44%	44%
Plasma	56%	36
Red blood count	4 000 000	4,300,000
Non protein nitrogen	29 mgm %	31 [illegible] %
Blood urea nitrogen	7 mgm %	7 mgm %
Cholesterol	190 mgm %	180 mgm
Blood sugar	80 mgm %	8[illegible] mgm
Serum chloride	390 mgm %	383 mgm %
Hinton test	negative	
Wasserman test	negative	
Urine		
Volume	8 11 liters	2 liters
Specific Gravity	1.001	1.0 0
Albumin	0	0
Sugar	0	0
Sediment	0	0

On March 8 1947 the patient became intoxicated and fell down stairs fractured his skull and died several hours later

Post mortem Report —Autopsy was performed 2 hours after death by Dr Timothy Leary The body was that of a well developed well nourished adult white male apparently of stated age Lividity was moderate Rigor mortis was not present There was a small abrasion in the occipital region and there was dried blood in both ears The pupils were round regular and equal measuring 4 mm in diameter There was no icterus of the skin or sclera The extremities were not remarkable There was a transverse scar on the neck cm above the sternal notch and a well healed McBurney scar on the abdomen

The peritoneal cavity was entirely normal except for a few fibrous adhesions between the duodenum and liver The pleural and pericardial cavities had smooth and glistening surfaces

Heart —Weight 350 grams The epicardium was smooth The myocardium showed slight scattered fibrosis The endocardium was not remarkable except for the mitral valve which was thickened and had adherence of the cusps with calcific deposits in the margins The chorda tendineae were thickened slightly and shortened The aortic valve was slightly thickened along the margins but there was no commissural adherence The tricuspid and pulmonic valves were not remarkable The coronaries were thin and pliable Measurements were tricuspid valve 10 5 cm pulmonary valve 7 5 cm mitral valve 7 3 cm aortic valve 7 5 cm left ventricle 0 7 cm 1 5 cm right ventricle 0 2 cm 0 4 cm

Lungs —Weight of right 435 grams of left 340 grams Both upper lobes were covered by large blobs and the upper portion of the right lower lobe likewise was bullous in appearance The color was grayish and both lungs were crepitant throughout Cut surface was grayish trebeculated and cystic in appearance in the upper lobes and dusky red in the lower with a very fine meshwork appearance The hilar nodes pulmonary vessels trachea and bronchi were not remarkable

The gastrointestinal tract spleen pancreas liver gall bladder adrenals urinary bladder and genital organs were entirely normal

Kidneys —Weight of right 160 grams of left 140 grams Cortex was sharply demarcated from the medulla and measured 4 6 mm in thickness The capsule was thin and stripped with ease leaving a smooth surface slightly marked by fetal lobulation The pelves ureters and hilar vessels were patent

The aorta was thin and pliable

The thyroid gland was not remarkable in appearance The parathyroids were not identified

Brain —See neuropathological report

Pituitary gland —Measured 1 × 0 6 × 0 4 cm

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Pituitary gland—Measured 1 × 0 6 × 0 4 cm

Middle ear —Fracture of the base of the skull extending from the occipital region into the right middle ear Left middle ear not remarkable

Bone marrow —Not remarkable

Microscopical Examination —Heart —There was a heavy deposit of calcium with fibrosis at base of mitral valve Epicardium was not remarkable Myocardium showed small foci of fibrosis located between bundles of fibres and in some areas within the bundles

Lung left upper lobe —The large blobs seen grossly appeared to be lined with a low cuboidal epithelium which in some places was thinned out to an endothelial like lining There was slight fibrosis beneath this and some of the smaller alveoli between these were filled with cellular debris *Lung left lower lobe* — Pleura was not remarkable Alveolar walls were thin but capillaries were somewhat engorged Alveoli contain many red blood cells and cellular debris

Liver —Slight dilation of central veins Parenchymal cells near periphery of lobules were moderately vacuolated

Kidney —Glomeruli showed increased nuclear elements Tubules were not remarkable except for a granular acidophilic material deposited in lumens Glycogen stain showed no deposits in tubules

Thyroid —Epithelium low cuboidal in type Acini were regular in size and shape and contained colloid darkly basophilic with smooth regular edges Interstitial fibrous tissue minimal

Adrenal —Cortex and medulla were well preserved and no abnormalities were noted

Pancreas —Acinar tissue was well preserved and without abnormalities Islands of Langerhans showed no fibrosis or degeneration

Testis —Active spermatogenesis was present Interstitial cells of Leydig appeared well preserved and were present in usual numbers

Bacteriology —Lung right lower lobe—no growth left lower lobe—B coli alpha hemolytic streptococcus

Neuropathological Report by Dr Raymond D Adams —There was a laceration of the scalp in the occipital region and reflection of the scalp disclosed an extensive subgaleal hemorrhage There was a linear fracture of the right occipital bone beginning just below the level of the tentorium extending down to the base of the skull and into the lateral portion of the petrous ridge of the right temporal bone There was no epidural hemorrhage but beneath the dura covering the left cerebral hemisphere there was a large non adherent clot dark red in color and of jelly like consistence covering the temporo parietal area This subdural clot had an estimated volume of 100 c c

Both cerebral hemispheres were swollen with flattening of the gyri and narrowing of the sulci more pronounced on the left side Over the posterior

and inferior surface of the right cerebellar hemisphere there was a layer of subarachnoid blood several mm in thickness Beneath this there was an area of laceration and contusion of the cerebellar hemisphere with hemorrhage and necrosis of the tissue to a depth of 3 cm beneath the surface

There was a large area of subarachnoid hemorrhage over the lateral and inferior surfaces of the left frontal and temporal lobes and beneath this there was extensive laceration and severe contusion of the frontal and temporal cortex Ecchymoses and petechial hemorrhages were seen at a depth

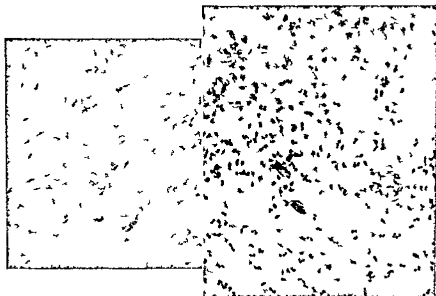


Fig 4 Supraoptic nucleus of patient with diabetes insipidus of idiopathic origin for 20 years showing nerve cell loss and gliosis (Nissl stain) left × 60 right × 30 Due to skull fracture there was much recent hemorrhage in adjacent tissues hence the hypothalamus was considerably distorted Consequently the tissue was not sectioned in exactly the same plane as the normal control

of 3 to 4 cm beneath the surface in these areas and there was a considerable amount of edematous swelling of the surrounding tissue

The ventricles were shifted to the right The left lateral ventricle was small the right enlarged There was herniation of the left cingulate gyrus and corpus callosun beneath the falx and small hemorrhages were seen in *these herniated structures*

There were several hemorrhages 3 to 4 mm in diameter in the midbrain and pons The pituitary was normal in size and shape and no abnormality was seen in the hypothalamic region

Microscopical Report—The posterior lobe of the pituitary gland was extremely small, in our best section it did not approximate even as much as ½ the normal size In the part of the posterior lobe which remained there were no significant changes the pituicytes were not altered and no other changes could be made out The anterior lobe was normal

There were many focal lesions and also diffuse changes in the hypothalmus The focal lesions were situated in the pre optic region in the general vicinity of the olfactory area in the anterior part of substantia nigra on each side and lateral hypothalamic nucleus In these there was a

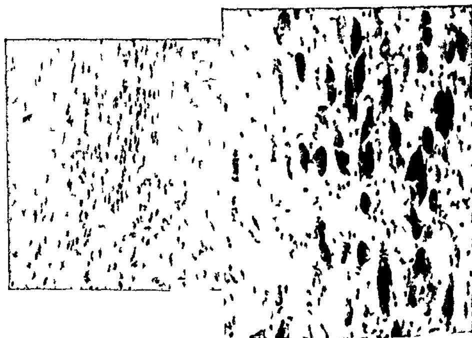


Fig 5 Normal supraoptic nucleus showing normal nerve cells in comparison with nerve cell loss and gliosis in the supraoptic nucleus in diabetes insipidus (Nissl stain) left × 60 right × 230

destruction of nerve cells many elongated microglial cells and microglial phagocytes containing a brownish pigment which gave a positive reaction for iron and was therefore probably hemosiderin and many enlarged astrocytes A few lymphocytes were collected in the perivascular spaces around veins especially

Most of the nerve cells in the supraoptic nucleus have disappeared (Fig 4) and numerous enlarged astrocytes were seen all through the nucleus There was moderate cell loss and astrocytic increase in the paraventricular nucleus on each side The ventro medial and dorso medial nuclei were

difficult to judge because there were several small fresh hemorrhages all through them There was probably slight cell loss here in the posterior hypothalamic and the mammillary nuclei There were no definite changes in the thalami the globus pallidus or putamen or the medial parts of the temporal lobes For comparison with Fig 4 see normal findings shown in Fig 5

There were many small hemorrhages in the lateral walls of the third ventricle These were made up of well preserved red corpuscles in which there were numerous neutrophilic leukocytes and capillaries with swollen endothelium

The pia arachnoid over the optic chiasm and the hypothalamus was thickened and excessively cellular The cells were chiefly fibroblasts with a few histiocytes and lymphocytes

Diagnoses—Laceration of scalp fracture right occipital and temporal bones subdural hemotoma left temporo parietal area subarachnoid hemorrhage laceration and contusion right cerebellum left frontal and temporal lobes multiple small foci of old hemorrhage and destruction of part of supraoptic nuclei lateral hypothalamic area and part of the substantia nigra recent small hemorrhage in the hypothalamus rheumatic heart disease old with mitral stenosis myocardial fibrosis and chronic passive congestion of lungs emphysema moderate both upper lobes diabetes insipidus clinical

Summary—At autopsy a fracture was found at the base of the skull involving the right occipital and temporal bones extending into the middle ear There was a massive subdural hematoma Also present was a healed rheumatic heart disease with mitral stenosis and myocardial fibrosis as well as a moderate bullous emphysema of both upper lobes Glycogen stains of the liver and kidneys showed no abnormal deposition of glycogen

At first examination the changes in the hypothalamus and substantia nigra resembled the lesions of lethargic encephalitis However the finding of blood pigment containing iron would indicate that these lesions are hemorrhagic Considering the character of the lesions with focal tissue destruction old hemorrhage and gliosis it seemed that trauma is a likely etiology with Wernicke s disease as a second less likely possibility However there was no old history of trauma The atrophy of the posterior lobe of the pituitary gland probably was secondary to degeneration of the supraoptic nuclei The anterior lobe was normal The diabetes insipidus was almost certainly due to destruction of the supraoptic nuclei and supra optic hypophyseal tract The hypothalamus and pituitary gland were not sectioned in the proper place for study of axis cylinders in supraoptic hypophyseal tract stalk and posterior lobe of pituitary gland by silver stain

Case II—A second case of diabetes insipidus of idiopathic origin on whom

an autopsy was performed in 1938 is reported through the cooperation of Dr H Edward MacMahon professor of pathology at Tufts College Medical School This patient was a 73-year old man who was known to have had diabetes insipidus for more than 5 years without any obvious etiology He had been married for many years He had one son who also had diabetes insipidus from birth and died at the age of 30 as a result of tuberculosis

The patient was always well in the past except that he had been somewhat obese He was a telegraphic operator and took very little exercise During the last few years of his life he had some elevation of blood pressure He drank large amounts of water day and night and was known to drink fabulous amounts of alcohol without having any appreciable intoxicating effects The physical examination was essentially negative except for his being obese Various laboratory data were negative The urine contained no albumin and no glucose and the specific gravity was always below 1 004 The patient finally developed cardiac failure and died

The autopsy findings are essentially irrelevant except for that which related to the size of the pituitary gland which was definitely smaller than normal The reduction was due mostly to diminution in size of the posterior lobe In addition the stalk of the pituitary gland was unusually thin flabby pale and pink The microscopical examination of the pituitary gland showed the usual proportion of the eosinophilic and basophilic cells to be maintained There was slight infiltration of the basophilic cells in the posterior lobe However this infiltration of the basophilic cells into the posterior lobe probably is a normal finding as Parsons[114] has pointed out that in advancing age there is an invasion of the posterior lobe of the pituitary gland by basophilic cells This increases with the age of the individual but shows no definite relationship to the average systolic or diastolic blood pressure In addition the arteries of the capsule showed thickening of the wall and replacement of the media by connective tissue with narrowing of the lumen The brain showed all the cerebral arteries to be markedly sclerotic with narrowing of the lumen without occlusion

The myocardium showed moderate hypertrophy The lungs showed bronchopneumonia The examination of the pancreas adrenals kidneys bladder gall bladder liver gastrointestinal tract were essentially negative The spleen showed some evidence of a toxic splenitis

Summary —This patient had had diabetes insipidus of unknown origin for over 5 years The post mortem examination showed that the pituitary gland was smaller than normal this was due chiefly to the marked diminished size of the posterior lobe In addition the pituitary stalk was unusually thin flabby and pink The cerebral arteries showed marked arteriosclerosis Studies of the supraoptic hypophyseal tract were not made probably because its clinical importance was not realized in 1938

Brain Tumors as Cause for Diabetes Insipidus

Tumors of the brain have been observed frequently to cause diabetes insipidus In our series it was the second most frequent cause with an incidence of 3[illegible] per cent of the 11[illegible] cases This frequency has been brought out particularly by Cushing

Brain tumors in patients with diabetes insipidus have been of various histological types and of various origins The disturbance resulting from them is caused either directly by destruction or injury to the supraoptic hypophyseal system by the tumor or by pressure of the new growth in this region Diabetes insipidus frequently has been an early manifestation of brain tumors and in a number of cases has preceded the pressure symptoms by many years A few cases with brain tumor on this account have been diagnosed first as idiopathic diabetes insipidus Occasionally repeated examinations of the eye grounds and the skull may result in the diagnosis of the brain tumor before the appearance of marked pressure symptoms Brain tumors producing diabetes insipidus frequently are accompanied by various endocrine disturbances which have been attributed often to the diabetes insipidus rather than to the encroachment of the tumor in the region of the brain which may cause these other disturbances Cushing[113] found that diabetes insipidus was the early symptom of brain tumor in children as young as three years of age

An analysis of the pathology of our cases with brain tumors is shown in Table II

As can be seen from Table II the tumors are of variable types and in locations which would produce pressure and involve the supraoptic hypophyseal system causing diabetes insipidus

The craniopharyngeal or suprasellar cysts and suprasellar meningiomas formed the largest group and were present in seventeen of the thirty six cases of brain tumor An x ray of the skull of such a case is illustrated in Fig 6 Third ventricle tumors occurred in eight cases

It was of unusual interest that in three cases pinealoma occurred simultaneously with a glioma of the third ventricle and of the chiasma These three patients were Italian Jewish and Scandinavian boys aged 13 to 17 years In a fourth case the diagnosis of pinealoma alone was made Such a coincidence also has been noted by others[110] The explanation of diabetes insipidus occurring in patients with tumors of the pineal body so far removed from the source of polyuria was not clarified until 1934 At that time Stringer[110] solved the role of pineal tumors in the

etiology of diabetes insipidus by finding a pinealoma as well as a solitary implant in the tuber cinereum in a case at necropsy

Martin and Davis[118] reported eight instances of diabetes insipidus in eighteen cases of pineal tumor They found implantations of the pineal tumors involving the pituitary body, the walls and floor of the third ventricle and the peri-aqueductal gray matter Horrax and Wyatt[116a]

TABLE II

PATHOLOGY IN 36 CASES OF DIABETES INSIPIDUS WITH BRAIN TUMOR

Pathology	*No of Cases*
Craniopharyngeal or suprasellar cysts	16
Suprasellar meningioma	1
Tumor 3rd ventricle	1
Glioma 3rd ventricle and chiasma	4
Glioma 3rd ventricle and chiasma and simultaneous pinealoma (1 case had congenital syphilis)	3
Pinealoma	1
Pituitary adenoma between legs of chiasma	1
Pituitary tumor	1
Interpedunculated cyst	1
Gliomatous cyst	1
Gliomatous cyst, cerebellum	1
Cyst pars intermedia	1
Angiomatous tumor at right of chiasma	1
Chromophobe adenoma of anterior pituitary gland	2
Tumor suspect	1
TOTAL	36

reported diabetes insipidus with ectopic pinealomas in the chiasmal region in three Jewish boys between 12 and 19 years of age In a further study Horrax[116b] noted five cases of diabetes insipidus in seventeen persons with pineal tumors Two of these five cases were verified histologically and the lesions in the other three were demonstrated by ventriculography In one patient the pineal tumor extended through the floor of the third ventricle involving the hypothalamus and pituitary body The other patient had an ectopic pinealoma in the area above the sella turcica

Besides these already mentioned there was a variety of other brain tumors in our series as shown in Table II The simultaneous occurrence

of a chromophobe adenoma of the anterior pituitary gland and an adenoma of the adrenal gland composed of cortical elements was of interest The adenomatous portions of the pituitary gland continued



Fig 6 X rays of 19-year old girl showing suprasellar cyst with calcification Sella is enlarged floor is depressed posterior clinoids are eroded

upward into the region of the third ventricle between the mammillary bodies and above the tuber cinereum In this case the diabetes insipidus could be caused by the pressure of tumor in the hypothalamus with possibly an increased function of the anterior pituitary gland resulting in polyuria

In Link's[111] study 68 out of 107 cases of diabetes insipidus had brain tumor Jones[117] found 13 cases of brain tumor in 4[illegible] cases of diabetes insipidus In our series of cases of diabetes insipidus the incidence of brain tumors 36 out of 112 cases was high because it reflected the interest of Dr Cushing in this disease

How soon symptoms of tumor will follow the onset of polyuria and polydipsia or vice versa cannot be predicted Long intervals have been observed In some of our cases the diabetes insipidus was the first symptom of tumor and preceded the onset of other symptoms by years For example one man aged 37 years had diabetes insipidus for as much as 21 years and visual disturbance for about a year before he was operated on for a suprasellar cyst In Nonne's[118] case diabetes insipidus was present in a child aged three years and 19 years later this patient died of a glioma at the base of the pons which compressed the diencephalon Another lengthy interval of this association was illustrated by Rosenbloom's case[119] in which the polyuria and polydipsia were present in a girl for 8½ years before the general symptoms of tumor were revealed The slow development of symptoms in such patients may be explained possibly on the basis that some tumors such as gliomas or suprasellar cysts grow very slowly However there have been cases of carcinoma and sarcoma reported in which the diabetes insipidus preceded death by as much as five years The polyuria and polydipsia may even disappear in some cases shortly before death as shown by Martin and Cushing[115], Wentzler[1] and von Hoesslin[1 0] Diabetes insipidus may disappear after operation according to Moffett[1 1] and on the contrary it may even increase after decompression as demonstrated by Cushing[1]

In six of our cases diabetes insipidus began as the result of operation for brain tumors The type of brain tumor present at operation is shown in Table III

The 36 cases of brain tumor discussed in this series were primary in the brain However there are metastatic tumors of the brain carcinoma[1] Hodgkin's disease and lymphoma, which may involve the pituitary region to cause diabetes insipidus

One of our cases not included under brain tumors was a man with lymphoma and diabetes insipidus who had been well until six weeks before admission to the hospital On his seventieth hospital day he developed a daily fluid intake and output of nine liters which were controlled by pitressin but not by radiation of the pituitary region He failed rapidly and died

TABLE III

PATHOLOGY OF 6 CASES OF DIABETES INSIPIDUS DEVELOPING AFTER OPERATION FOR BRAIN TUMOR

Case	Sex	Age Years	Pathology	Comment
1	F	6	Craniopharyngeal cyst	Died years after operation
	F	6	Craniopharyngeal cyst	Died 2 years after operation
3	M	8	Craniopharyngeal cyst	Died 1 month after operation
4	F	40	Craniopharyngeal cyst	Diabetes insipidus developed 19 days after operation and disappeared 12 days later shortly before death
5	F	56	*Suprasellar meningioma*	*Died 3 months after operation*
6	M	5	Craniopharyngeal cyst	Diabetes insipidus developed a few months after operation 12 years ago and has persisted Is now 17 years old and quite well but there has been no sexual development

Post mortem examination showed malignant lymphoma throughout the lymph nodes in various parts of the body The pituitary gland revealed in its center tumor cells yellowish gray in color and similar to those tumor cells found in the other organs One portion of the pituitary contained a large tumor which infiltrated the normal anterior lobe In the midst of the tumor were clumps of compressed and degenerating anterior lobe cells There was extension beyond the capsule of the pituitary

A case of Hodgkins disease with a daily urine volume of 15 liters was reported by Desbuquois[15] who attributed the polyuria to metastatic tumor of the pituitary gland or surrounding areas Glycosuria was found also in this case and treatment with insulin and posterior pituitary extract relieved both conditions

Syphilis as Cause of Diabetes Insipidus

Syphilis was a comparatively frequent cause of diabetes insipidus in the old days and in our cases before 19 5 Oppenheim[14] emphasized this relationship by showing that in 36 cases of syphilitic meningitis 1 had diabetes insipidus Syphilis was the third most common cause of diabetes insipidus in our 112 cases occurring in seven instances or 6 per cent of the cases studied The central nervous system syphilis was acquired in five cases and congenital in two cases An eighth case had congenital

syphilis but the cause of the diabetes insipidus in this instance was a glioma of the third ventricle and pinealoma existing simultaneously Syphilis occurred in 14 cases or 13 per cent of the 107 autopsies studied by Fink[111] The lesions were either a basal meningitis or gumma in or near the hypophysis

Most cases of syphilis causing diabetes insipidus are acquired and few appear to be congenital It is difficult to tell in some instances whether these 2 diseases occur by coincidence or whether there is a relation between them The cases of diabetes insipidus which improve with antisyphilitic treatment obviously would appear to be due to syphilis Nonne[118] reported a case in which the syphilis was in the nature of a calcified gumma in the pituitary gland

Cases with mild diabetes insipidus and syphilis have been reported by Drouet and Hamel[115] In these the urine output was three to four liters a day Yet on the other hand there are severe cases of diabetes insipidus associated with syphilis with an output ranging from eight to 15 liters[116] Diabetes insipidus and syphilis may occur at almost any age even as early as two years In the cases of syphilis the Wassermann and Hinton tests usually are positive and in a few there is a family history of the disease Miscarriages stillbirths or early death among the patients relatives have been reported In our cases the spinal fluid showed the characteristic findings of central nervous system syphilis

Trauma as Cause of Diabetes Insipidus

Trauma to the head as a cause of diabetes insipidus has been stressed frequently It was not uncommon as noted by Fink[111] Yet when one considers the tremendous number of injuries to the head and the rarity with which diabetes insipidus occurs it appears that in most cases the history is coincidental unless the injury to the head is unusually severe

Zenker[117] observed diabetes insipidus only 4 times in -,800 cases of injury to the head However the incidence was higher in the cases of basal skull fracture three of his four cases occurring in -50 cases of skull fracture Pickles[117] also found only four cases of diabetes insipidus in over 2 500 patients with head injuries In three the diabetes insipidus cleared up within 1½ to 4 months after the injury The fourth case had polyuria and polydipsia of short duration and it was not known whether the symptoms would be permanent Since lesions in the region

of the pituitary gland and associated structures led to diabetes insipidus it is probable that basal skull fractures cause this condition either by hemorrhage injury or by the formation of scar tissue in that area Porter and Miller (466) noted 13 cases of diabetes insipidus in 5 000 persons with non fatal closed head injuries admitted to a military hospital in Oxford England In these cases the symptoms usually were noticed 2 or 3 weeks after the injury and spontaneous recovery took place in the majority within 9 months Trauma has been reported as the etiology of diabetes insipidus in some cases which later were proven to be due to tumors or other lesions

Diabetes insipidus supposedly may appear almost immediately after the injury or after months or even years later The duration of the polyuria and the polydipsia cannot be predicted because some cases recover in a short time while others become permanent

A case which illustrates some of these points is that of a 21-year old girl who was thrown from a horse and struck on the back of her head Shortly thereafter she was admitted to the hospital in considerable pain She was conscious but had a temporary loss of taste and smell

X-rays of the skull showed 2 fractures of the occipital bone and one extending from the bottom of the sella into the sphenoid bone A lumbar puncture showed grossly bloody spinal fluid The laboratory tests otherwise were irrevelant Two days after the accident her fluid intake increased to 6 300 c c and then four days after the injury the fluid intake decreased to 2 600 c c as shown in Fig 7 The fluid intake and output then remained at a normal level

It is now five years since the injury and the patient has remained free of polyuria and polydipsia This case represents one of temporary diabetes insipidus resulting shortly after a severe fracture at the base of the skull

Although diabetes insipidus may follow severe trauma to the head trauma should not be taken for granted as the cause of this disease Some cases have given a history of trauma with concussion of the brain and unconsciousness for hours or a day but finally at operation years later the lesion was found to be a brain tumor I am not convinced from our cases that trauma is as frequent a cause of diabetes insipidus as was believed formerly

Another form of trauma recently noted which may result in temporary diabetes insipidus is pre frontal lobotomy[1 8] performed for certain types of mental disease The exact mechanism for this complication is

syphilis, but the cause of the diabetes insipidus in this instance was a glioma of the third ventricle and pinealoma existing simultaneously Syphilis occurred in 14 cases or 13 per cent of the 107 autopsies studied by Fink[111] The lesions were either a basal meningitis or gumma in or near the hypophysis

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The effect of pituitrin on the symptoms of diabetes insipidus due to trauma is variable In certain cases there is a marked reduction in the fluid intake after pituitrin injections while in other instances the results are variable

Encephalitis as Cause of Diabetes Insipidus

Diabetes insipidus due to encephalitis may be caused by a variety of infections When encephalitis is preceded by an acute contagious disease the polyuria and polydipsia presumably are produced by a complicating encephalitis *Warkany and Mitchell*[132] *in a review found that encephalitis* with resultant diabetes insipidus had occurred as a sequel to influenza measles scarlet fever whooping cough diphtheria chicken pox and even after vaccination

Measles was the etiology of Findlayson s[133] case of diabetes insipidus which persisted during eight years of observation Kulz[129] and Blatt and Greengard[134] observed scarlet fever to be the precursor of persistent diabetes insipidus in children as young as four years of age Cases in which pertussis preceded diabetes insipidus have been reported by Gayler[135] Turner[136] and Dimeri[137] Diabetes insipidus following diphtheria subsided spontaneously after three months in Whittle s patient[138] Flandin and associates[139] noted *the onset of diabetes insipidus a few weeks after* an attack of mumps in a man aged 28 years The testes were not involved Salmi s case[140] of diabetes insipidus complicated varicella Roehm[141] *observed postvaccinal encephalitis in a boy who seven days after vaccination* developed headache fever chills and persistent thirst One of our cases was a 51 year old woman who had had diabetes insipidus for *46 years beginning immediately after vaccination against small pox at* the age of five years

Diabetes insipidus may be a complication of postencephalitic Parkinson s disease *The time of onset of the polyuria and polydipsia after the* encephalitis varies Diabetes insipidus began a year or two after the onset of encephalitis in our two patients In the pathological study by Fink[111] encephalitis rarely was found The degree of polyuria *and polydipsia* and the effect of pitressin differ considerably in these individuals

Leprosy too may produce encephalitis and resultant diabetes insipidus Davis[142] gave a unique report of such a case in an 8 year old African leper girl whose parents were lepers It is interesting that

not known However, it points to involvement of the basal ganglia and hypothalamic system

Other surgery of the brain also may produce diabetes insipidus For example Riser and associates[129] noted the occurrence of this in a 62 year old woman who immediately had intense polyuria in the course of ablation of a recurrent opto-chiasmic cyst Yet, on the other hand Kourilsky and associates[130] discussed post-traumatic diabetes insipidus and noted the sudden cessation of thirst during the incision of an arachnoid cyst of the opto-chiasmal region with resultant recovery Their case was that of a woman aged 2_ years who had had a fractured

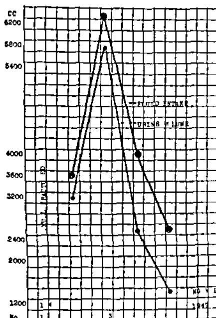


Fig 7 Temporary diabetes insipidus occurring in a girl shortly after skull fracture

skull four years previously and diabetes insipidus which began after she had regained consciousness Four years later, when the cyst was incised and fluid drained, the patient said she had no thirst

In six of our cases diabetes insipidus developed following operations for brain tumor It was interesting that five of the six cases were craniopharyngeal cysts while the sixth was a suprasellar meningioma It is very difficult to avoid interference with the supraoptic-hypophyseal system because of the location of these tumors Possibly young females are more susceptible to such damage since four of the six cases were females

entity xanthomatosis In 1921 he[148] published a second case and altered the diagnosis in his first case to xanthomatosis Schuller[149] in 1915 described *two cases under the name of hypophyseal dysostosis* because he considered the pituitary responsible for this syndrome In 1919 Christian[4,10] published his classical study of a case which really made known this clinical entity Since then the name of Christian's disease has been used by *many In 19 the disease was noted in an adult by* Hochstetter[151] and in a child by Griffith[11] Autopsy of the child showed that



Fig 8(a) Case of Christian's disease showing the extensive moth eaten appearance of the skull, in 1918

the posterior lobe of the hypophysis was replaced by fibrous tissue and xanthomatosis Subsequently there have been a number of cases reported particularly in recent years

The signs and symptoms of this syndrome depend on the systemic and the local effect of the lipoid disturbance Diabetes insipidus is the third most common symptom of Christian's disease occurring in 61 of 103 cases of xanthomatosis in children *reviewed by* Atkinson[13] The first most frequent sign of the disease is bony changes in the skull and the second exophthalmos

Schuller suggested that the cause of this syndrome was due to the posterior lobe of the hypophysis Schultz *Wermbter and Puhl*[152] be

diabetes insipidus[113] as well as other major endocrine disturbances[114] is unusually rare in Africans

Tuberculosis as Cause of Diabetes Insipidus

A tuberculous process involving the pituitary gland and its surrounding structures at the base of the brain may produce diabetes insipidus In Fink s[111] study the lesion in five of 107 necropsies was due to a tuberculoma or tuberculous meningitis Tuberculosis as the etiology of this disease appears more in the older than in the recent literature I have never seen a case of diabetes insipidus due to tuberculosis although in one case a boy inherited diabetes insipidus from his father but died of pulmonary tuberculosis at the age of 30 years However, there have been cases in other series in which tuberculosis was the accepted cause of diabetes insipidus Healy[145] described such a case in a 2-year old boy whose mother had pulmonary tuberculosis At autopsy there were miliary tuberculosis external hydrocephalus and replacement of the pituitary gland by caseous tuberculous material The pituitary gland in von Hann s[61] case was involved likewise by a tuberculous process On the other hand tubercles may affect the infundibular region and not the pituitary gland to produce diabetes insipidus Hagenbach[116] and Haushalter and Lucien[14] studied such cases in which tubercles were found in the infundibular region at autopsy These patients were children with a family history of tuberculosis The prognosis in the past has been poor but with the modern treatment of tuberculosis improvement possibly may result

Xanthomatosis as Cause of Diabetes Insipidus

Xanthomatosis is a comparatively rare and unusually interesting cause of diabetes insipidus It consists classically of defects in bones, exophthalmos diabetes insipidus and frequently arrested development However, these signs are not always present at the same time There are about 15 synonyms of this disease including Schuller Christian Hand s disease, Christian s disease and general granulomatosis

Hand[118] in 1893 presented a case of polyuria which he believed to be due to tuberculosis not realizing he was dealing with a new clinical

swollen and tender When she was 3½ years old the right eye became prominent and she began to have polydipsia and polyuria The symptoms gradually increased until both eyes were markedly protruding and she was drinking nine quarts of water a day and urinating every hour



Fig 9 Case of Christian's disease in 1930 showing spontaneous healing of skull bones

The physical examination at that time showed an underdeveloped and poorly nourished girl The striking features were marked bilateral exophthalmos and defects in the cranial bones through which the

lieved that the primary lesion was a hyperplasia of the reticulo endothelial system while Rowland[155] showed later that the disturbance was due to lipoid cell hyperplasia of this system Hand had suggested that the cause for this lesion was an infection because some cases followed an infectious fever The pathology of this syndrome has been studied from various aspects including lipoids[156], foam cells[1 7] and lipoid granulomatosis[1 1 9]



Fig 8(b) Case of Christian s disease showing the extensive moth eaten appearance of the skull in 1918

Christian's case presented a truly remarkable picture which is given briefly here

This patient a 5 year old girl born July 31 1912 was studied in 1918 at the Peter Bent Brigham Hospital She had been well until the age of three years when her teeth began to decay and her gums became

pounds Because of the previous history of pyelitis and fever at operation she was immediately given penicillin therapy The temperature became normal for five days before discharge After operation the daily fluid intake and output ranged from three to seven liters which were relieved with pitressin She left the hospital against advice on October 26 1944 and did not take good care of herself The x rays of the skull in 1944 were much the same as in 1930 The pelvis by measurements was considered adequate for an average small baby

On November 2 1944 she was admitted to a mental hospital because of an acute psychosis She died November 13 1944 at the age of 3[illegible] years of general septicemia due to pyelitis and postpartum psychosis no autopsy was made The baby is now five years old and growing normally She appears to be healthy with normal bone development

Most observers believe that the disease is a disorder of lipoid metabolism resulting in hypercholesteronemia which gives rise to hyperplasia of the reticulo-endothelial system and xanthomatous cells are substituted for the normal tissue the hypophysis playing a secondary part I believe that the pituitary gland plays a primary rather than a secondary role in the disease because there is a disturbance in lipoid metabolism both in xanthomatosis and in diabetes insipidus[18] when they occur as independent diseases Furthermore the administration of posterior pituitary solution modifies the blood cholesterol levels following a fat meal[16] In one of our cases the blood cholesterol was normal In another the increased blood cholesterol was decreased by pituitrin therapy as shown in Table IV

TABLE IV

PLASMA CHOLESTEROL LEVELS OBTAINED IN A PATIENT WITH XANTHOMATOSIS RECEIVING 500 CC 20% CREAM WITH AND WITHOUT PITUITRIN THERAPY

Plasma cholesterol levels mgm per 100 c c plasma

	Hours after fat test meal				Comments
Fasting	2	4	6	8	
275	184	184	88	7	no pituitrin
225	237	2[illegible]8	223	220	on pituitrin

Eosinophilic Granuloma as a Cause of Diabetes Insipidus

A condition which appears related to Christian s disease is eosinophilic granuloma the former representing the gravest form and the latter

pulsations of the brain could be felt The neurological and ophthalmoscopic examinations were normal The polyuria decreased with pituitary therapy

X-ray revealed most extraordinary pictures showing extensive defects of the skull bones as illustrated in Figs 8(a) and 8(b)

Christian compared the defects of the skull to the irregular holes in a bit of motheaten flannel It was suggested that a disturbance in the secretion of the pituitary gland was responsible for the defects in the bones particularly because the diabetes insipidus was controlled by the injection of pituitary substance although it had no effect on the exophthalmos

Sosman[159] in 1930 studied Christian's case The story went as follows During the next five years after seeing Dr Christian the patient gradually improved, attended school and developed normally In 1930 it was found by palpation and x-ray examination that all the defects in the skull and pelvic bones had healed completely The exophthalmos was still present but slight in degree The diabetes insipidus was less marked than previously Menstruation began at 16 and was normal She stated that she had no treatment after leaving the hospital and that the skull defects closed when she was about 13 years of age The urine and blood analyses were normal

The roentgen examination showed normal epiphyseal development for her age The skull as illustrated in Figure 9 however by x ray was peculiar in that the anterior fossa appeared shortened, thickened and depressed The posterior fossa and occipital area were by comparison overly-developed There was a peculiar backward slant to the frontal bone The mastoids were sclerosed, and there were two malposed unerupted teeth in the lower jaw In 1930 she was in her second year of high school and was leading a healthy normal life

I followed up her case recently The patient continued to be well and the diabetes insipidus apparently disappeared for about 10 years until two years ago when it reappeared She graduated from high school in 193- and later was employed in a plant as a plastic worker She progressed normally and had no trouble with her bones However in the past two years she has had polyuria and polydipsia again and also frequent episodes of euphoria and depression She married on June 13 1942 She went through a normal pregnancy except for pyelitis On October 8 1944 a cesarean section was performed because of a placenta praevia with hemorrhage She was delivered of a normal baby girl weighing five

pounds Because of the previous history of pyelitis and fever at operation she was immediately given penicillin therapy The temperature became normal for five days before discharge After operation the daily fluid intake and output ranged from three to seven liters which were relieved with pitressin She left the hospital against advice on October 26 1944 and did not take good care of herself The x rays of the skull in 1944 were much the same as in 1930 The pelvis by measurements was considered adequate for an average small baby

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TABLE IV

PLASMA CHOLESTEROL LEVELS OBTAINED IN A PATIENT WITH XANTHOMATOSIS RECEIVING 500 CC 10% CREAM WITH AND WITHOUT PITUITRIN THERAPY

Plasma cholesterol levels mgm per 100 c.c plasma

	Hours after fat test meal				Comments
Fasting	2	4	6	8	
75	184	84	89	7	no pituitrin
225	237	2 8	223	210	on pituitrin

Eosinophilic Granuloma as a Cause of Diabetes Insipidus

A condition which appears related to Christian s disease is eosinophilic granuloma the former representing the gravest form and the latter

the mildest expression of the same pathological process. Various authors have reported on the pathology of this syndrome[161]. Thoma[161] described such a case which was accompanied by diabetes insipidus. His patient was an 8-year old child with a recurrent swelling of his lower jaw. Two years previously a swelling had appeared under the right jaw which increased gradually in size until operation six months later. After operation the right side remained fairly normal but swelling appeared two to three months later on the left side. All the front lower teeth became loose and displaced. During the previous year the patient voided five to seven liters daily. He responded normally to pituitrin therapy.

X-rays of the entire skeleton showed numerous irregular and clean cut defects in the mandible with no reactive bone around them. There were small circular defects in the right parietal bone. The skeleton elsewhere was normal except for minute defects in the left pubic bone. A biopsy of the left mandible showed eosinophilic granuloma.

X-ray treatment of the jaws and sella turcica resulted in repair of the defects. There was no improvement of the diabetes insipidus following x-ray therapy of the skull.

Renal Rickets and Diabetes Insipidus

Renal rickets or renal dwarfism is associated rarely with diabetes insipidus. Yet polyuria and polydipsia frequently are associated with renal rickets as shown by the fact that they occurred in 40 out of 72 cases of renal rickets studied by Maddox[16] and in 64 out of 78 cases of renal dwarfism reviewed by Mitchell[16]. Polyuria was observed usually at the time of weaning and was especially prominent under the age of three years. It has been suggested that the simultaneous occurrence of the renal rickets and polyuria is caused by lesions in the pituitary diencephalon region resulting in a pituitary dysfunction.

Charnock[163] believed that the renal, the parathyroid hypertrophy and the pituitary-diencephalon theories explained the etiology of the coexistence of the two diseases. Gittleman and Pincus[161] found that the pancreas and the pituitary were the only glands of internal secretion showing evidence of dysfunction in these cases. Others concluded that this condition resembles that of hyperparathyroidism. It is believed that the pituitary gland is responsible for the genital urinary tract defects.

Bieber[165] described a case of diabetes insipidus and renal rickets with grave renal calculosis. Bader[166] reported similar cases in two brothers aged

nine years and less Moehlig's[187] case of renal rickets associated with diabetes insipidus was quite interesting His patient was an intelligent small boy five years old with retarded development Enuresis had been present since birth At the age of 10 months he drank large quantities of water during the day and night The physical examination showed a



Fig 0(a) Skull in a case of renal rickets with diabetes insipidus showing intracranial pressure and flattening and elongation of sella turcica

small boy with bilateral papilledema and marked genu valgum The urine had a specific gravity of 1 002 to 1 006 and contained albumin

Diodrast given intravenously showed very low concentration of the dye but it appeared in ten minutes in the pelvis and calices of only the left kidney following injection of the dye There was incomplete outlining of the kidney pelvis and calices

The x rays of the skull were of the hydrocephalic type with evidence of increased intracranial pressure and flattening and elongation of sella turcica as shown in Figure 10(a) The daily fluid intake and output ranged from 2 670 to 4 680 c c which diminished with pituitary injection



Fig 10(b) Hand in a case of renal rickets with diabetes insipidus

Cerebral Hemorrhage Cerebral Arteriosclerosis as Cause of Diabetes Insipidus

In the old days cerebral hemorrhage was a fairly common factor in the etiology of diabetes insipidus As far back as 1865 Leyden[164] re

ported a case of a 30 year old patient who developed a daily urine volume of six to eight liters six weeks following cerebral apoplexy. Ollivier[164] later called attention to the frequency of such cases. I observed one case of diabetes insipidus which followed a cerebral hemorrhage with hemiplegia.

On the other hand, certain types of hemorrhage of the brain may alleviate diabetes insipidus. Loewenberg and Sloane[165] reported such a case of a 38 year old man with diabetes insipidus of 20 years duration which improved following a spontaneous arachnoid hemorrhage. The hemorrhage possibly was due to a rupture of a small aneurysm of the circle of Willis. He was in the hospital for four weeks and the diabetes insipidus gradually improved. During the subsequent 7 months he was in good health. Apparently the intact aneurysm caused pressure at the base of the brain in the pituitary hypothalamic region and removal of the pressure by hemorrhage caused an amelioration of the symptoms.

Pellagra as Cause of Diabetes Insipidus

Diabetes insipidus may be a comparatively frequent concomitant of pellagra. Although the symptoms of diabetes insipidus in the majority of the cases are mild, the excretion of urine ranges from four to seven liters with a low specific gravity. According to Rassulev[illegible] approximately 25 per cent of the patients with pellagra have polyuria and polydipsia. He reported a normochloremic and hypochloruric type of diabetes insipidus in this disease. Diabetes insipidus ordinarily appears in advanced pellagra several weeks or months after the onset of the disease. However, the polyuria and polydipsia disappear gradually with the improvement of the pellagra. On the contrary, Spies[illegible] saw only one case of diabetes insipidus among many persons with pellagra.

Miscellaneous Causes of Diabetes Insipidus

There are other conditions which may result in diabetes insipidus. I observed a 10 year old boy who had diabetes insipidus apparently related to granulocytic hypoplasia of the bone marrow, hypoplasia of lymph nodes and bilateral cryptorchidism with hypoplasia of the testes. The pituitary gland was very small. There was an area of focal necrosis in the distal part of the anterior lobe. This boy had complained of weak

ness and pallor for two months before admission A month before admission polyuria and polydipsia developed During his stay in the hospital he had a fever of 100 to 101 F Marked secondary anemia was present with a white blood count of 2,000 to 3,000 and a differential of 29 per cent polymorphonuclears, 62 per cent lymphocytes, 4 per cent large mononuclears and 1 per cent eosinophils

Other rare causes of diabetes insipidus with post mortem reports are actinomycosis[171], hydrocephalus of idiopathic origin[172], leukemia[173] and absence of the hypothalamic pituitary system[174] Sheldon[175] had a 20 year old patient with lymphatic leukemia as a cause of diabetes insipidus Autopsy revealed diffuse lymphocytic infiltration of the pituitary gland In Kugelmeier's[176] case of myelogenous leukemia diabetes insipidus developed suddenly as a result of septic necrosis of the posterior lobe and stem of pituitary body One of our cases was an 18 year old girl who had diabetes insipidus in the terminal state of myeloid leukemia She had a daily fluid intake of eight to ten liters for nine days before death

Sarcoid Schauman s disease Besnier-Boeck s disease benign lymphogranulomatosis) may cause diabetes insipidus Lesné and associates[177] presented a case of diabetes insipidus occurring in the course of Besnier Boeck's benign lymphogranulomatosis who had a digital sarcoid X-rays showed cysts or cystoids of digits They believed that this disease in the form of nodules existed at the base of the brain causing diabetes insipidus Tillgren's case[178] was a 42-year old man with Schauman's disease In the middle lobe of the pituitary gland there were characteristic epithelioid foci without necrosis and with inconsiderable lymphoid reactions In some foci there were giant cells which Schauman found in lesions of lymphoid organs

Brucellosis[179] rheumatic disease[180], malaria[181] progressive muscular dystrophy[182] whooping cough[183], tetanus typhoid and typhus osteitis fibrosa polycystica[184, 185] and multiple myeloma[186] all have been reported as the etiology of the disease Chorea with subsequent encephalitic syndrome appeared to be the cause of diabetes insipidus in two of our cases One, a 13-year old boy had had St Vitus dance ½ years previous to the onset of polyuria and polydipsia The second case was a 22 year old girl who at the age of 14 years had had severe St Vitus dance which was followed by diabetes insipidus

The case of multiple myeloma was a 51-year old farmer who for one year had a daily urine volume of 3½ gallons loss of 44 pounds of weight and pain in many bones X-rays of skull, ribs vertebrae femur

and pelvis showed extensive destruction with peculiar moth eaten appearance

Flinker's case[18] of diabetes insipidus and progressive muscular dystrophy is of unusual interest because of the possible relation of the pituitary gland to certain myopathies His patient was a 16 year old girl who had been well until eight months previously when she developed simultaneously progressive muscular dystrophy and diabetes insipidus

In this connection too there is the unusual case (467) of Laurence Moon Biedl syndrome with diabetes insipidus Legg Perthes disease and Telford Smith finger

Kidneys and Other Organs in Diabetes Insipidus

There were 15 post mortem studies made in these cases As far as can be determined from examination there was no obvious gross or microscopic lesion in the kidney to cause diabetes insipidus Kidneys somewhat larger than normal have been reported The disturbance in the kidney in diabetes insipidus is one in its function or the pathological physiology which already has been described in detail However Marie[187] considered diabetes insipidus as a disorder of permeability of cellular membranes of the nephron hypopermeability to water and maintained permeability to sodium chloride However in one instance a 16 year old girl with diabetes insipidus and diabetes mellitus for years was found to have hydro-ureters and hydro-nephrosis Another patient a 51 year old man with diabetes insipidus for years had renal calculi After removal of the calculi the diabetes insipidus improved appreciably There is no specific pathological change as far as can be determined in other organs of the body Any such change appears secondary or coincidental with the lesion producing diabetes insipidus

Various organs such as the heart lungs thyroid pancreas gastro intestinal tract liver spleen adrenal and sex glands have been found to be normal at autopsy One case with brain tumor also showed an adenoma of one adrenal gland

Thyroid Gland — The thyroid gland in three cases of diabetes insipidus who had total thyroidectomy were studied more thoroughly microscopically and chemically The glands weighed from 16 5 gm to o gm In two of the cases there was evidence of hyperactivity The thyroid gland showed a slight increase in fibrous tissue as represented by

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scattered trabeculae deep gray in color but the intervening thyroid parenchyma was a pale tan with a deep red cast Colloid was within normal limits On microscopic examination the thyroid showed a few small follicles but most were of normal size with the usual amount of colloid Follicles occasionally showed high cuboidal epithelium although most of the epithelium was low cuboidal and occasionally flat Some of the follicles lined with high cuboidal epithelium contained little colloid and others showed slight papillary projections The stroma was scant There was slightly more than the usual degree of vascularity

In view of abnormal levels of the blood and urine iodine in diabetes insipidus discussed under laboratory studies the total quantity of iodine was determined in the thyroid glands of two patients with this disease whose thyroids were removed surgically in total thyroidectomy As control tests the iodine content was determined in the normal thyroid glands of two cardiac patients who had total thyroidectomies for the relief of cardiac decompensation In the patients with diabetes insipidus there was 402 mgm of iodine per gm of wet tissue and the total amount of iodine in the whole thyroid glands was 6 96 mgm and 8 22 mgm In the control thyroid glands there were 605 mgm and 500 mgm iodine per gm of wet tissue, and the whole of these glands contained 11 1 mgm and 15 0 mgm respectively These findings suggest that there is a decreased amount of iodine in the thyroid gland of patients with diabetes insipidus

Mucous Membranes—The mucous membranes of the mouth in patients with diabetes insipidus were normal in color and texture Although the mouth was comparatively dry from diminished salivary output there was some moisture from the buccal mucous gland secretion Biopsies of the soft palate and gingival papillae in several cases were normal histologically

Etiology

Idiopathic Origin

The etiology of diabetes insipidus is varied In 50 of our 112 cases of diabetes insipidus the etiology was idiopathic However, it is important to note that two boys, aged 24 and 19 years included in the group with diabetes insipidus of idiopathic origin gave the history that the polydipsia developed during the course of treatment for Vincent's infec

tion of the teeth Possibly the chemical used in the treatment of the infection in these cases may have produced a toxic effect on the supra optic hypophyseal system

Pathological Conditions

In 36 cases various types of brain tumor were the cause of diabetes insipidus Syphilis caused the disease in seven cases Infections of various types have been the etiological factor in some instances In certain investigations heredity has been found to be an important cause A number of other causes of diabetes insipidus has been claimed These are discussed under Pathology However any disease which produces a lesion in the supraoptic hypophyseal system may cause diabetes insipidus

Heredity

Heredity is not regarded ordinarily as a cause of diabetes insipidus Nevertheless in reviewing the literature there are reports which show that diabetes insipidus may be inherited and transmitted through many generations of a family I have observed for 11 years a boy with diabetes insipidus whose mother and grandmother had the disease[188]

One of the most illuminating reports on the inherited tendencies or the familial characteristics of diabetes insipidus is that given by Weil[189] and his son[190] In 1884 when Adolph Weil[189] was professor in Heidelberg he studied four generations of a family of 91 members headed by a man with diabetes insipidus and found that 24 of these had the disease Later in 1908 his son Alfred Weil[190] continued his father's studies and found that in five generations of this family there were 35 cases of diabetes insipidus among 220 members Two-thirds of the cases were men and one third women A number of these patients lived to a very old age For example two daughters who had had the disease their entire lives were 87 and 92 years old The possibility of inheritance of diabetes insipidus was known as far back as 1841, when Lacombe[191] reported its occurrence in five males and three females in two generations of a family Trousseau[19] and Lanceraux[193] too commented on the familial tendencies of the disease in several patients

Certain accounts by authors on the number of persons affected with

diabetes insipidus in various generations of individual families may be presented as follows one to three cases in one generation[193, 194, 195], two to six cases in two generations[196, 197, 198, 199, 200, 201] seven to eight cases in three generations[202, 203] and five to eleven cases in four generations[204, 205, 206]

Other observations on this phase of the diabetes have been made by McIlraith[207], who presented three familial cases, two of which were brothers The third case was a boy whose three brothers mother maternal grandmother and an aunt were affected Chase[208] traced diabetes insipidus through five generations of a family which appeared remarkable in that in the fourth generation as many as 10 out of 23 children had the malady Chester and Spiegel[209] studied the family of a woman with polyuria whose father, paternal grandmother, maternal grandmother and a maternal aunt were similarly afflicted Curiously one child of the woman's first marriage and one of the second marriage had diabetes insipidus Gansslen and Fritz[210] saw a patient with an ulcer of the stomach and diabetes insipidus whose history revealed that he as well as his only son had had the disease since early youth and that no amount of scolding or beating by the patient's parents could make him stop drinking water In addition they studied the family tree of a very large family by delving into the records of births deaths and marriages for seven generations which went back to about 1700 They found that the disease was carried through each of the last five generations affected with diabetes insipidus Levit and Pesslova[211] found three cases of familial origin out of their 16 cases of diabetes insipidus

A most interesting study was made more recently by Ellerman[12] who was consulted in 1937 by a man aged 23 years with diabetes insipidus since childhood The man explained that a brother as well as his father and grandfather also had this syndrome Further inquiry revealed that this family had been studied by Lauritzen[10] in 1893, when it was discovered that nine of the 15 members had the disease In 1938 this family had 73 members of whom 26 (11 females and 15 males) were found to have polyuria Ellerman's records indicated that the majority of these patients had a daily diuresis of from 12 to 16 liters while in others it was less severe amounting to from four to nine liters He believed that the mode of hereditary diabetes insipidus seemed to be one of simple dominance

Bulloch[13], Just[14] and Hogben[15] discussed the inheritance of the disease from certain selected references in the literature without adding any of their own cases Bulloch[13] presented some detailed outlines and

charts of each family tree to which he referred In addition there have been other contributions to this study[216, 17, 218, 19]

The following is a report of a family under my observation

Son—This patient is a 31 year-old bright single man of Scandinavian descent whom I have observed for approximately 11 years His history aside from his diabetes insipidus is irrelevant The family history is important because his mother and grandmother also had this clinical entity He has never had any brothers or sisters His father died of heart disease at the age of 48 when the patient was 6 months old The patient has had diabetes insipidus since infancy and was a bottle fed baby His mother noticed that just as soon as he could walk and reach for water he drank all he could get and was always after it As he grew older he imbibed as much as 3 or 4 gallons of water a day Most of our observations have shown that his daily fluid intake and output have been about 10 to 12 liters Pituitrin administered intramuscularly or intransally in sufficient amounts reduced the polyuria and polydipsia to normal

The physical examination showed a well developed and well nourished young man with no abnormal findings His height was 6 feet and his weight was 193 pounds A number of laboratory examinations were made and found to be normal

Mother—The patient s mother is a 51 year old widow She has consumed much water since childhood and always took a quart or more to bed with her up to 10 years ago At 41 the time of her menopause her diabetes insipidus improved and now she takes daily about 5 or 6 liters of fluids Except for the polyuria and the polydipsia she has always been quite healthy She had no difficulty with the pregnancy or with the birth of her son her only child She had one brother who died of tuberculosis at the age of 24 Another brother died in infancy of unknown cause She had no sisters Her father is 75 years old and quite well

Her general physical examination has been normal Her height is 5 feet 5½ inches and her weight was 135 pounds

Grandmother—The grandmother was a woman who drank more than 2 gallons of water a day when she was a girl She too took a quart or more to bed with her until the age of 60 However she improved at the age of 40 about the time of her menopause but she still had polyuria and polydipsia at 64 when she died of chronic myocarditis and coronary disease She had 4 brothers 1 of whom died of diabetes mellitus Her height was 63 inches and her weight was 165 pounds

A review of our 112 patients with diabetes insipidus revealed only three inherited cases In addition to the two already presented there was another case of a boy who had polyuria since infancy He inherited the disease from his father who had diabetes insipidus for more than 25

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Bulloch[213], Just[214] and Hogben[215] discussed the inheritance of the disease from certain selected references in the literature without adding any of their own cases. Bulloch[213] presented some detailed outlines and

insipidus genes One of his interesting findings was the time of the first appearance of diabetes insipidus in a group of males who inherited the disease The time of onset of thirst and polydipsia begin anywhere from the age of about two weeks to the age of three years Most of them recalled that it had begun very early in life One case was noted to have drunk large amounts of fluids since birth In general it seems definite that the thirst was observed most often during the first year of life The mother noticed most that these children sucked more eagerly at wash cloths and drank their bath water Their crying at night could be quieted only with water

Diabetes Insipidus in Twins

The occurrence of twins in families with diabetes insipidus is unusually rare There were no cases of twins with diabetes insipidus reported by Weil[1] and his son[1] and by Forssman[2 1] in their extensive studies on the inherited tendencies of this disease On the other hand Harding described eight cases of diabetes insipidus and of these two cases were identical twin girls both having had diabetes insipidus with normal growth and development The father grandfather and father s sister all had diabetes insipidus One of the identical twins was pregnant and died from cerebral anoxia resulting from spinal anesthesia Post-mortem examination showed that she had an adenoma of the anterior portion of the pituitary gland

During the course of my investigations I [3] found that one patient an 18 year old boy had a non identical twin sister who did not have diabetes insipidus There was a striking contrast between these twins They differed markedly in stature general configuration and progress of growth

Comparative Development of the Twins —John s Record —John has been under my observation since he was 5½ years when he first developed diabetes insipidus He was born 10 minutes before his twin sister Each baby weighed seven pounds at birth and was of normal height The delivery like the pregnancy was normal and was performed at home without instruments The patient had a healthy infancy and gained moderately well He developed his first tooth at six months and walked at 15 months His childhood diseases consisted of measles mumps and chicken pox About six months before the onset of the diabetes insipidus he had hurt his head and the question arises as to

years The son finally developed tuberculosis and died at the age of 30 years Inheritance was questionable in another patient whose mother probably had mild diabetes insipidus

Diabetes insipidus is a disease which may be inherited and transmitted through many generations of a family through the maternal or paternal side to either male or female children When this disease is inherited it may be found rather frequently in such a family Inherited diabetes insipidus occurs ordinarily more often in males than in females and sometimes slips a generation only to appear in the next The birth of children with the disease to normal mothers, one of whose parents had diabetes insipidus suggested to some authors that the transmission of polyuria at times simulated that of hemophilia

Inherited diabetes insipidus may appear shortly after birth or later in life For example, Klaften[2 0] reported that a 24 year old woman with diabetes insipidus for 21 years gave birth to an apparently normal baby who at the age of four weeks already took more fluids than normal On the other hand the two brothers and sister of the family presented by Clay[191] all developed the disease at the age of nine years

Polyuria which develops later has been said not to be present at birth[09] The kidneys in infants play a comparatively minor role in the regulation of water exchange, the important factors being the skin and gastrointestinal tract When the children are about two years old the kidneys add the function of regulation of water balance in addition to their function of excretion of metabolic wastes At this same age the symptoms of hereditary diabetes insipidus are most likely to appear

There is a rather general impression that familial diabetes insipidus is due to a dominant gene This view was based chiefly on the study of the large family presented by Weil Levit and Pessikova[211] believed that there is a questionable validity in drawing conclusions from select rather than comprehensive material gathered from the literature as done by Bulloch because it creates the impression that practically every case of polyuria is a familial one They concluded that the development of familial diabetes insipidus is due to a conditionally dominant gene showing poor penetrance However, I believe that, once diabetes insipidus has been shown to be inherited by a person, there is a good possibility that this individual may pass the disease on to some of his offspring

Forssman[1] published a 196-page article on hereditary diabetes insipidus based on an extensive geneological study covering 5 500 subjects and five pedigrees with a total of 83 known carriers of diabetes

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whether the injury had played any part in the precipitation of the disease The family history was irrelevant X-ray studies of the skull were negative

At the beginning of the disease, John's daily fluid intake and output were three to four liters When he was 11 years old, the volume without pituitary therapy was about six to seven liters and at present is about nine to ten liters Pituitary extract administered intranasally or intra muscularly always has reduced the amount of urine to normal

When John reached the age of eight his mother noticed that he was not growing so fast as his twin sister and with the lapse of time this difference in weight and height became more marked The boy did well in his studies until his second year in high school when he had to with draw because of poor work

At 18 his physical development was still retarded He had not matured sexually he did not have to shave The lad had also become extremely sarcastic Six months later however there was a considerable improvement John showed marked sexual changes and his voice now was deeper There was a beginning growth of hair on his face and a large amount of pubic hair although it had a female distribution The penis was 5 inches long and he had daily erections, the testes too, were normal in size

His physical examination was not remarkable except for his stunted growth When he was 14 years of age his basal metabolic rate was −9 per cent

Joan s Record — Joan s birth was normal and she had a healthy childhood with a normal growth and maturity A tall well built attractive girl she is now about a head taller and 25 pounds heavier than John She was bright in her studies and graduated from high school at the age of 17 years She has a pleasant personality in contrast to John During her childhood she had much the same diet as her twin brother

Her menses began when she was 13 years and have been regular and normal The basal metabolic rate of Joan at the age of 14 was −19 per cent Physical examination was entirely negative

Table V presents a record of progress of the twins height and weight at two year intervals

Comparative X-ray Studies of Twins —When the twins were 14 years old x ray films of the skull and right hand and wrist were obtained to determine whether there was any difference in their bony develop ment The reports were as follows

TAPLE V

RECORD OF HEIGHT AND WEIGHT OF TWINS

	John		Joan	
Age Yrs	*Height in*	*Weight lbs*	*Height in*	*Weight lbs*
6	44	39	43	42
8	46	46	48	53
10	49	51	53	65
1	51	56	56	71
14	55	64	61	9
16	58	6	63	10
18	62	85	66	111

Films of John s skull are normal In the film of the right hand and wrist all the epiphyses are wide open as shown in Fig 11

Films of Joan s skull show it to be normal and 0 8 cm greater in anteroposterior diameter than that of her twin A film of the right hand and wrist showed that the epiphyses of the terminal phalanges are closed and the others maturing in other words there is a difference of two or three years in bone age

At the age of 17 years the twins were X rayed again the reports are as follows

Re examination of John s skull shows it to remain normal Re-examination of the right hand and wrist shows all epiphyses open with not even the expected changes of maturation The findings indicate a definite delay in epiphyseal union

Re examination of Joan s skull shows it to be normal Re examination of the right hand and wrist shows all epiphyses closed and the bones normally developed

A comparison of these two sets of films shows there has been no appreciable growth of the skull in either case During this three year period however John s bones had definitely grown being 1 cm longer from the base of the third metacarpal to the tip of the finger His epiphyseal development on the other hand is delayed Apparently Joan s development was earlier

X ray films of John at the age of 18½ years showed no change in the cranial vault or in the sella The mandible appeared slightly larger and heavier The right hand and wrist showed only slight changes which indicated beginning maturation of the epiphyses particularly at the proximal end of the proximal phalanx of the middle finger All the epiphyses were still open and the growth had not yet ceased (see Fig 11)

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Her menses began when she was 13 years and have been regular and normal The basal metabolic rate of Joan at the age of 14 was −19 per cent Physical examination was entirely negative

Table V presents a record of progress of the twins height and weight at two year intervals

Comparative X ray Studies of Twins —When the twins were 14 years old x-ray films of the skull and right hand and wrist were obtained to determine whether there was any difference in their bony development The reports were as follows

TABLE VI

112 Patients With Diabetes Insipidus Due to Various Causes

Sex	No of Cases
Male	61
Female	51

36 Patients With Diabetes Insipidus Due to Brain Tumor

Sex	No of Cases
Male	23
Female	13

76 Patients With Non Brain Tumor Diabetes Insipidus

Sex	No of Cases
Male	38
Female	38

Age Incidence

Diabetes insipidus may be recognized at any period from infancy to old age In my group of cases the two youngest patients began to have diabetes insipidus at birth and at the age of seven weeks The oldest patient is living and quite well at 8 years and she was 60 years old when the disease started The disease occurs most frequently in persons under 40 years of age It is commonly observed in children about two or three years of age and higher A number of the patients examined when they were adults knew that they had had diabetes insipidus since childhood Diabetes insipidus is not discovered accidentally as diabetes mellitus often is Patients with diabetes insipidus come to the doctor with the specific complaint of polyuria polydipsia and severe thirst The degree and severity of the diabetes insipidus may be the same in children as in adults that is it may be either severe or mild at any age period

The present ages of the 112 cases due to various causes ranged from 13 months to 82 years Ninety eight of these patients were below 45 years of age while only 14 were aged 46 to 82 years In a study of the age of onset of the 11 cases it was of particular interest to note how much the incidence of diabetes insipidus shifted to the lower ages The age at onset of the disease in these cases is appreciably less than that

In summarizing the above findings one can emphasize that the striking feature is the marked difference in the development of these twins Of particular significance is the fact that John who had diabetes insipidus showed a stunted growth and lack of development in his bone structure These signs however are not always necessarily found in patients with diabetes insipidus Where they do occur it appears that they are the result of a disturbance in the anterior pituitary gland

Incidence

Diabetes insipidus is a rare disease as revealed by hospital records It occurred in only 17 instances among 75 941 or one in 4 469 consecutive cases admitted to the wards of the Beth Israel Hospital in Boston At the Peter Bent Brigham Hospital the incidence was twice that at the Beth Israel Hospital due to the interest which Cushing and others had in brain tumors and this disease There in approximately 155,000 admissions diabetes insipidus occurred in 78 cases or one in 2 000 of which 32 resulted from brain tumor At the Mayo Clinic[24] from 1910 to 19 4 there was reported an incidence of one per 7 600 cases The unusually rare incidence of one in 50 000 cases was found at the Montreal General Hospital before March, 19 1

Apparently the incidence of the disease has not increased in the past three quarters of a century In clinics in Zurich [6] and Berlin [7] from 1876 to 1896 diabetes insipidus occurred once in 5 000 and [illegible] 000 cases respectively, while in the medical wards of the Johns Hopkins Hospital [8] there was one per 2 800 cases from 1889 to 1904

Sex Incidence

A study of the sex of patients with diabetes insipidus is shown in Table VI

Of the 112 patients with diabetes insipidus due to various causes 61 were males and 51 were females It has been pointed out in the literature that diabetes insipidus affected men more often than women and that also it affected more boys than girls In 76 non brain tumor cases the disease was equally common in the females and in males In those due to brain tumor there were 23 males and 13 females

TABLE VI

112 Patients With Diabetes Insipidus Due to Various Causes	
Sex	No of Cases
Male	61
Female	51

36 Patients With Diabetes Insipidus Due to Brain Tumor	
Sex	No of Cases
Male	23
Female	13

76 Patients With Non brain Tumor Diabetes Insipidus	
Sex	No of Cases
Male	38
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Age Incidence

Diabetes insipidus may be recognized at any period from infancy to old age In my group of cases the two youngest patients began to have diabetes insipidus at birth and at the age of seven weeks The oldest patient is living and quite well at 82 years and she was 60 years old when the disease started The disease occurs most frequently in persons under 40 years of age It is commonly observed in children about two or three years of age and higher A number of the patients examined when they were adults knew that they had had diabetes insipidus since childhood Diabetes insipidus is not discovered accidentally as diabetes mellitus often is Patients with diabetes insipidus come to the doctor with the specific complaint of polyuria polydipsia and severe thirst The degree and severity of the diabetes insipidus may be the same in children as in adults that is it may be either severe or mild at any age period

The present ages of the 112 cases due to various causes ranged from 13 months to 82 years Ninety eight of these patients were below 45 years of age while only 14 were aged 46 to 82 years In a study of the age of onset of the 112 cases it was of particular interest to note how much the incidence of diabetes insipidus shifted to the lower ages The age at onset of the disease in these cases is appreciably less than that

TABLE VII

AGE OF ONSET AND PRESENT AGE OF 112 CASES OF DIABETES INSIPIDUS DUE TO VARIOUS CAUSES

Ages	*Age of Onset No of Cases*	*Present Age No of Cases*
at birth	1	—
7 weeks	1	—
1 year	2	1
2 years		—
3 10 years	20	8
11 18 years	6	6
18 2 years	9	10
3 8 years	8	3
38 45 years	11	21
46 59 years	7	10
60 8 years	1	4
? age	4	—
Total	112	112

when they were first observed because the disease had been present in many of the cases for a number of years The incidence of the ages at onset and at present of the various cases of diabetes insipidus are shown in Table VII

The ages of the patients with diabetes insipidus due to brain tumor were considered separately because there was an appreciable number of them 36 cases The ages of these individuals too were comparatively low three fourths of the patients with brain tumors were below 38 years of age as shown in Table VIII

TABLE VIII

AGE OF ONSET AND PRESENT AGE OF 36 CASES OF DIABETES INSIPIDUS DUE TO BRAIN TUMOR

Ages	*Age of Onset No of Cases*	*Present Age No of Cases*
3 10 years	7	4
12 18 years	14	13
20 2 years	2	—
23 38 years	4	10
40 43 years	3	5
45 59 years	3	4
? age	3	—
Total	36	36

Nationality Incidence

The incidence of the nationalities in this study of 112 persons with diabetes insipidus of various causes is of striking interest to me. The Jews appear to have the highest incidence of diabetes insipidus which occurred in 35 of the 112 cases. The Old Americans were next in order with 31 cases. Next came the Italians and the Irish who had 16 and 10 cases respectively. Then were the Greeks, Scandinavians, Scotch, Germans, Hungarians, French, Portugese, Lithuanians and Argentinians each with from four to one cases in this group. Just how to account for the high incidence of diabetes insipidus in the Jews I do not know. Certainly it is not due to the fact that there were 17 cases of diabetes insipidus at the Beth Israel Hospital, because of those only 12 were Jewish.

In the study of the nationalities as commonly understood there is no doubt some inaccuracy in determining them. In the study of the brain tumor cases the incidence of the nationalities of the Old American, Jewish, Irish and Italian were much the same as the proportions found in the general run of cases. The other nationalities listed were rather infrequent and consequently no definite opinions can be drawn from so few cases. The nationalities of the 112 patients are shown in Table IX.

TABLE IX

NATIONALITY OF 112 PATIENTS WITH DIABETES INSIPIDUS DUE TO VARIOUS CAUSES

Nationality	*No of Cases*	*% of Cases*
Jewish	35	31
Old American	31	8
Irish	16	14 3
Italian	10	9
French	4	3 6
Greek	3	7
Danish	4	3 6
Scotch	3	2 7
Lithuanian	2	1 8
German	1	9
Hungarian	1	.9
Portuguese	1	.9
Argentinian	1	.9
Total	112	

Symptoms

General Symptoms

The cardinal symptoms of diabetes insipidus are persistent polyuria, polydipsia and severe unquenchable thirst. An ordinary case of diabetes insipidus has a marked polyuria during the day and night, and most cases excrete from 10 to 12 liters of a very pale, watery urine in 24 hours. The symptoms may appear at any time from infancy to old age.

The thirst in most cases is so severe and the mouth so dry that the patients require an intake of large volumes of water amounting to 10 to 1[illegible] liters daily. In some cases the fluid intake and output are much greater and may rise to as much as 47 liters. The fluid intake in general closely parallels the urine volume. I am familiar with the case of a 17 year old boy with a fluid intake and output of 32 to 37 liters which one day reached the enormous volume of 47 liters. On the other hand there are mild cases with a daily volume of about five liters. In some cases a much greater fluid intake and output occur at the onset than in later periods of the disease. For example, there is a common history of drinking 15, 20 or 25 quarts of water in a day at the onset of the disease, and later the volume decreases and remains at a level of about 10 quarts.

The symptoms of the disease are continuous and persist during the day and night. If a patient is able to sleep through the night without having thirst, polydipsia or polyuria, it is quite certain that he does not have diabetes insipidus.

The onset of the symptoms of the disease usually is acute, occurring frequently at a specific hour which the patient often remembers. This is true particularly in the cases of idiopathic and of traumatic origin. In the latter instance, however, the polyuria may be only temporary.

A school teacher with the disease told me that she could compare the desire for water to the craving for food by starving victims. The undue need for some fluid to drink is beyond the understanding of a normal person. As a result she advised and stressed that patients do as they feel like and drink water and take medication when and where they desire. A patient knowing that he can not get water until a certain time finds the need all the greater.

She remembered that her polyuria and polydipsia started suddenly one day almost simultaneously, although perhaps the polyuria came first. In a day or two she realized something was really wrong. She thought perhaps she had eaten salty food and was thirsty and then had to urinate

If the fluid intake is restricted it results in severe torture of the patient Cases have been reported in which a restriction in the water intake has led a patient to drink his own urine in order to satisfy to some extent the thirst

Although the polyuria is said to occur at birth and the symptoms of the disease may appear in patients at about the age of two years in certain instances parents acquainted with the disease through inheritance may tell by about the sixth month whether or not the infant will have diabetes insipidus

In infants the disease becomes noticeable because the child is not satisfied with the amount of fluid he ordinarily receives and cries as soon as he is removed from the breast or when the bottle feeding is finished If this thirst is mistaken for hunger he may be given additional food and diarrhea may result from this chronic overfeeding However the condition in many of these infants is recognized because of the frequent wetting during the day and night compared with the ordinary amount that an infant will wet

This disease in some children is recognized when they are going to school and it is observed that they have to leave the room frequently to void In rare cases there has been enuresis which disappeared as the children grew older Enuresis is not present in adults

In other cases like those due to slow growing brain tumors or infections such as syphilis or post encephalitic Parkinson s disease the onset of the diabetes insipidus seems to be rather gradual and the patients note finally that they are drinking considerable amounts of water and voiding considerable quantities of urine In rare cases the diabetes insipidus is said to start after an emotional upset

I have seen the polyuria and polydipsia decrease in a number of cases during febrile attacks In unusually rare instances the symptoms of the disease have disappeared spontaneously

Nowadays the matter of thirst polyuria and polydipsia is not a great problem because the patients may be treated satisfactorily with pituitary extract by one method or another In certain cases the drinking of water is a pleasure and some drink from 11 to 1 liters of water a day and seem to enjoy it without any ill effects For example one boy who is now 30 years old inherited the disease and does not take pituitary extract During the war he was in the coast guard without commenting that he had the disease and went through the war without any difficulty at all He enjoys drinking water frequently and does not mind getting up four or five times during the night to void

In some cases the quenching of the thirst is not limited to the drinking of water I have seen a number of cases where the patients would consume large amounts of alcohol either in the form of whiskey or beer Many of these people remark how they can take these large quantities of alcoholic liquors without suffering from alcoholic intoxication However experimental evidence makes me wonder why they do not have alcoholic symptoms because the alcohol content of their blood and urine is much the same as in the normal person following a given dose of alcohol These experiments will be discussed later

In addition to the classical symptoms of diabetes insipidus there are a number of secondary symptoms related to the disease The secondary symptoms depend on the underlying cause and complications of the disease For example if a patient has post encephalitic Parkinson s disease he will have the symptoms of that disease together with polyuria and polydipsia

If a patient has a brain tumor producing diabetes insipidus any of the symptoms and signs of the brain tumor in its particular location will complicate the picture The outstanding symptom of the patients who have diabetes insipidus due to brain tumor, is failing vision This complication is understandable when one realizes the close relationship between the supraoptic hypophyseal tract and the optic chiasma Any patients with diabetes insipidus who complain of failing vision, should be suspected strongly of having a brain tumor Other symptoms are diplopia headache dizziness loss of weight, weakness and impotence

In rare cases there are other glandular or endocrine changes aside from the pituitary gland disturbances Symptoms of those endocrine glands which are involved may be irregular menses or amenorrhea, impotence Frohlich s syndrome underdevelopment of the genitals retarded growth and development or delayed epiphyseal union Amenorrhea and irregular menses could be explained on the basis of an associated hypofunction of the anterior pituitary lobe involving the gonadotropic factors and not on the basis of posterior lobe insufficiency The libido and sex functions in the uncomplicated cases of diabetes insipidus are normal and in some instances increased during therapy with pituitary extract

A few patients have an inferiority complex and appear below par socially Rarely one is mentally retarded The patients who have had diabetes insipidus of idiopathic origin for years seem to adjust themselves well and pursue a comparatively normal life

It is said that patients with diabetes insipidus perspire very little even

after exercise However the ones I have observed through the years seem to perspire normally

There have been some reports indicating an improvement of symptoms during puberty However I have not seen any cases improve during or after puberty If anything it seems that the total intake of fluid and the output of urine increase until the patient has reached his normal final stature size and weight In other words when the height and weight remain constant the fluid intake and output do not appear to increase

There are some factors such as exercise and diet which appear to cause some slight changes in the fluid intake Exercise increases the thirst while rest tends to decrease the fluid intake However in general when a patient takes daily about 10 or more liters of fluid and passes about the same amount of urine these volumes will not vary much under most any circumstances

Duration of Symptoms

The history of the duration of the diabetes insipidus in 112 cases of this disease due to all causes ranged from one day to 46 years as illustrated in Table X

In most cases the disease was present for years and in 30 cases it was present for as much as 7 to 46 years It is surprising how many of them were able to get along well before the days of pituitrin in spite of the

TABLE X

DURATION OF DIABETES INSIPIDUS DUE TO ALL CAUSES IN 112 PATIENTS

Duration	*No of Cases*
1 day	1
1 4 weeks	7
2 5 months	11
6 18 months	25
2 5 years	26
7 18 years	19
21 38 years	9
45 46 years	2
Post-operative (brain tumor)	5
Duration ?	7
Total	11

fact that they were disturbed even in their sleep due to the necessity of voiding and drinking In five cases the disease started almost immediately after a brain tumor operation The literature records patients who have had the disease for more than 45 years

The duration of the diabetes insipidus due to brain tumor was interesting because many patients had the disease for years, even as long as 5 years, as shown in Table XI

Special Symptoms

There are various special symptoms related to the untreated cases of diabetes insipidus The commonest of these are associated with the mouth teeth salivary secretion and the gastrointestinal tract

Teeth, Mouth and Saliva in Diabetes Insipidus —In observing a comparatively large group of patients with diabetes insipidus for many years I have been impressed with the high incidence of caries and false teeth in young patients with this disease It has been known clinically in the untreated cases of diabetes insipidus that the mouth is dry and that a small amount of tenacious saliva is secreted The administration of pituitrin tends to produce the opposite effect It has also been shown in a study of 14 patients with diabetes insipidus, who were examined orally that there was apparently a high caries rate attack

With the more modern knowledge of the relation of caries to saliva it was important to study a group of patients with diabetes insipidus from this point of view

TABLE XI

DURATION OF 36 CASES OF DIABETES INSIPIDUS DUE TO BRAIN TUMOR

Duration	*No of Cases*
1 4 weeks	3
4 18 months	11
5 years	9
9 1 years	4
21 5 years	2
Post operative for brain tumor	5
Duration ?	2
Total	36

The volume and specific gravity of the saliva were obtained in the patients after they chewed paraffin for 15 minutes and had expectorated all the activated saliva into test tubes during this period. The experiments were carried out when the patients were untreated and again after the administration of pituitrin. The measured salivary output in the untreated patients is unusually low.

The highest caries attack rate appeared in those who showed a diminished salivary output. The development of caries in these patients probably was accelerated by a lack of saliva which caused the particles of food to cling to the teeth. Several investigators[38] have shown that extirpation of the salivary glands in animals greatly increased the susceptibility to caries. An interesting aspect of salivary output in diabetes insipidus is the relation of the thirst mechanism to salivary output. Some of the patients with larger amounts of saliva were as thirsty as those secreting a smaller amount. The patients having nearer the normal salivary outputs showed a reduced susceptibility to caries.

When a group of patients with diabetes insipidus was untreated, the volume of saliva secreted during the 15 minute period was unusually small, ranging in volume from 1.5 to 4.5 c.c., with specific gravity of 1.000 or 1.001. In contrast, after the injection of pituitrin in these patients the salivary secretion during the test period increased markedly to volumes ranging from 13.0 to [illegible]5.0 c.c., but the specific gravity remained constant at a level of 1.000 or 1.001.

Illustrations of the results in seven cases are shown in Table XII.

This finding in saliva is in contrast to the action of pituitrin on the volume and specific gravity of urine whereby the volume is decreased

TABLE XII

VOLUME AND SPECIFIC GRAVITY OF SALIVA IN PATIENTS WITH DIABETES INSIPIDUS CHEWING PARAFFIN DURING A FIFTEEN MINUTE PERIOD

	On Pituitrin		No Pituitrin	
Case	*Volume c.c.*	*Specific Gravity*	*Volume c.c.*	*Specific Gravity*
1	25.0	1.000	4.0	1.000
2	16.0	.001	1.5	1.000
3	13.0	1.000	1.6	1.000
4	24.0	1.001	4.5	1.000
5	12.0		2.9	
6	25.2	1.001	3.3	
7	21.7	1.001	3.1	1.001

fact that they were disturbed even in their sleep due to the necessity of voiding and drinking In five cases the disease started almost immediately after a brain tumor operation The literature records patients who have had the disease for more than 45 years

The duration of the diabetes insipidus due to brain tumor was interesting because many patients had the disease for years, even as long as 25 years, as shown in Table XI

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With the more modern knowledge of the relation of caries to saliva it was important to study a group of patients with diabetes insipidus from this point of view

TABLE XI

DURATION OF 36 CASES OF DIABETES INSIPIDUS DUE TO BRAIN TUMOR

Duration	*No of Cases*
1-4 weeks	3
4-18 months	11
[illegible]5 years	9
9-1[illegible] years	4
21-25 years	2
Post operative for brain tumor	5
Duration ?	—
Total	36

mouth and of the nasopharynx to the point of anaesthesia failed to control the polyuria or the polydipsia Further evidence to substantiate this idea is illustrated by cases of xerostomia This peculiar condition is characterized by suppression of the secretion of the salivary and buccal glands, dry oral mucous membranes dry tongue but no polydipsia or polyuria There is also increased caries of the teeth, of a type similar to that seen in diabetes insipidus Pilocarpine has been injected[3] in patients with diabetes insipidus to produce increased salivary secretion but no increase in salivary output or diminution of thirst occurred Normally pilocarpine decreases thirst and increases salivary secretion which may amount to one half liter or more in the course of 2 or 3 hours after an injection of the drug The skin and lungs also excrete normally even a larger quantity of fluid during the same time It appears that thirst in diabetes insipidus is more than the mere expression of dryness of the mucous membranes of the mouth

Gastric Symptoms and Gastric Analyses in Diabetes Insipidus – Indefinite gastric symptoms such as nausea vomiting heart burn retching and poor appetite appeared to be a common complaint in patients with diabetes insipidus especially in the morning when no pituitrin had been administered for several hours Most patients with this disease have had varying amounts of abdominal cramps following treatment with pituitrin given by injection This type of symptom however has largely disappeared when at present so many of the patients with diabetes insipidus take pituitrin intranasally or pitressin tannate in oil by injection

These complaints led to a study to determine whether there were any unusual changes in the chemistry of the gastric juice and in the gastrointestinal x rays in eight patients with diabetes insipidus who had marked gastric symptoms[32] This investigation was made by studying the gastric analysis and the proteolytic activity of the gastric juice in six patients with and without pituitrin administration Gastrointestinal x rays were obtained in five cases Alcohol orally and histamine subcutaneously were used as stimulants for gastric juice Proteolytic effect was studied by noting the effect of gastric juice on coagulated egg albumin The rennin activity was determined by noting the effect of various dilutions of gastric juice on the clotting of milk

The results of gastric analyses obtained with the alcohol test meal in patients with diabetes insipidus showed that in the tests without pituitrin therapy there appeared to be a greater amount of gastric juice and free HCl than is customarily found in normal people following such a

and the specific gravity markedly increased One might expect an elevated specific gravity of the saliva with its low volume in untreated diabetes insipidus and a low specific gravity with a large volume of saliva after the injection of pituitrin Apparently in diabetes insipidus pituitrin acts as a stimulant of the saliva as a whole and not only of its water content

The marked decrease in the salivary output in diabetes insipidus may be appreciated more when the results are compared with those obtained in normal individuals under the same conditions In the normal person the volume of saliva during the 15 minute test period was approximately 25 to 30 c c without pituitrin and 15 to 20 c c with pituitrin each with a specific gravity of 1 000 to 1 001 as shown in Table XIII

This result is comparable with a low volume of 1 5 to 4 5 c c with the same specific gravity in untreated diabetes insipidus Furthermore the injection of pituitrin in the normal person decreased the volume of saliva just the opposite of its action in diabetes insipidus

The mucous membranes of the mouth were dry and histologically normal when the volume of saliva was low The tongue appeared parched at times The dryness disappeared when the volume of saliva was large after pituitrin therapy In general the thirst disappeared with pituitrin therapy, but there were some patients who still had some peculiar sensation in the mouth which they would have liked to quench with water

According to Starling[31] normal saliva when secreted is nearly neutral with a pH of 6 4 to 7 0 and with a specific gravity of 1 002 to 1 008 The saliva in the patients with diabetes insipidus was also nearly neutral as in the normal

Attempts have been made to determine the role of local sensation in the mouth with regard to water intake and urinary output in diabetes insipidus Apparently local nervous influence has been excluded as a cause of thirst because cocainization of the mucous membranes of the

TABLE XIII

VOLUME AND SPECIFIC GRAVITY OF SALIVA IN NORMAL PEOPLE CHEWING PARAFFIN DURING A 15 MINUTE PERIOD BEFORE AND AFTER THE INJECTION OF PITUITRIN

Normal Person	*No Pituitrin* Volume c c	*No Pituitrin* Specific Gravity	*On Pituitrin* Volume c c	*On Pituitrin* Specific Gravity
1	30.4	1.000	19.6	1.000
2	24.6	1.001	15.9	1.000

patients the x rays revealed a duodenal ulcer These cases may be of interest because of the possible relations between certain brain lesions and peptic ulcer The diabetes insipidus was of idiopathic origin in these cases

The cause of the gastric symptoms in many of the patients with diabetes insipidus is conjectural However from the results of these experiments patients with diabetes insipidus appear to have following certain stimulation a greater volume of gastric juice with a higher degree of acidity and an increased pepsin and rennin content than in the normal person The injection of pituitrin inhibited these effects Because of these findings it would seem that the posterior lobe of the pituitary gland has some control over the gastric secretion As a result of a lack of posterior lobe secretion in diabetes insipidus there is an increase in certain constituents of the gastric juice These findings fit in with some observations of Dodds and associates[35] who found in animals that the stimulating effect on gastric secretion by various stimuli is abolished by an extract of the posterior lobe of the pituitary gland The volume of juice is primarily affected These authors found that the response to histamine in hypophysectomized animals differed markedly from normal and concluded that the role of a substance secreted by the posterior lobe of the pituitary is essential for the normal regulation of gastric secretion In addition DeAncia es[36] found that pituitrin decreased the gastric secretion with its acid content in normal persons Since recent studies in gastroenterology infer a correlation between certain cerebral lesions and gastrointestinal disturbances it may be suggested that the neurological lesions of diabetes insipidus may cause gastric symptoms Water intoxication as a cause of gastric symptoms should be considered here Nevertheless I do not believe it is the cause of this disturbance because three of my patients with a fluid intake and output of about 8 or 9 liters a day have not taken pituitrin for 2 or 3 years and they have had no stomach complaints Furthermore the blood chlorides have been normal in these cases

Very little or no peptic activity of the gastric juice occurred after the alcohol test meal in these patients This was in striking contrast to the marked peptic digestion by the gastric juice obtained in the patients after the histamine injection even though the acidity and the volume of gastric juice produced by both gastric stimulants were much the same

Further evidence that in diabetes insipidus the pituitary gland is primarily at fault in producing gastric symptoms has been suggested strongly by the work of Kaulbersz and associates[37] It has been shown

test meal The administration of pituitrin decreased the acidity of the gastric juice during the test period and also diminished its volume one hour after the injection of the drug There was no obvious digestion of the egg albumin, with few exceptions at the end of 24 or 48 hours in most of the specimens of gastric juice whether or not pituitrin was administered Since I[31] have shown that alcohol inhibited the proteolytic activity of gastric juice it appeared that the alcohol might account for some of these results although it did not seem likely as late as one and one-half or two hours after the ingestion of this dilute alcohol The alcohol appeared to stimulate a good amount of acid but not proteolytic enzymes

It was then determined whether another type of gastric stimulus would produce different results Consequently histamine was used and these findings were interesting In the tests without pituitrin histamine produced a large volume of gastric juice with a high degree of acidity and marked proteolytic activity in most specimens These findings were definitely more marked than in the control tests in normal people The gastric juice from patients without pituitrin caused a marked or complete digestion of the egg albumin in most instances

In the patients with marked gastric symptoms the rennin test was positive in many of the specimens in a dilution of 1 80 000 of gastric juice The degree of acidity and of rennin and peptic activity did not always run parallel In contrast in the normal controls the rennin test usually was positive in dilutions of gastric juice ranging from 1 1 000 to only 1 8 000

The administration of pituitrin shortly before the testing decreased the gastric acidity and either the peptic or rennin effect in both patients with diabetes insipidus and in the normal individuals In general there was a greater amount of digestion when pituitrin was not administered

In comparing the results of the gastric analysis in the patients with diabetes insipidus following the alcohol test meal and the administration of histamine it is obvious that these two drugs stimulated the volume and acidity of the gastric juice to about the same extent However histamine produced gastric juice with a marked proteolytic effect whereas alcohol did not

X-rays of the gastrointestinal tract in five patients with marked gastric symptoms without pituitrin therapy were normal in three cases The esophagus appeared normal The stomach was smooth in outline with good peristalsis and no residue in six hours after the ingestion of the barium The duodenal cap ileum and cecum were normal In two

polyuria was controlled but the patients continued to have a compulsion thirst and drink large amounts of water resulting in water intoxication with convulsions. In one case there was laboratory evidence of some dilution of the blood, while in two cases there was no such evidence.

Experiments[3] were carried out in dogs given large quantities of water by mouth following the administration of pituitary extract. These resulted in marked tremor, salivation, vomiting and finally convulsions and coma. Large amounts of water alone given to the dogs did not produce untoward signs or symptoms. Blood volume determinations were made before the administration of pituitary extract as well as before consumption of large amounts of water and again after the onset of the symptoms. No appreciable changes were found in the blood volume before and after water intoxication.

The cause of water intoxication in these cases is questionable. Hydremic plethora as a cause was considered but no increase in the total blood or plasma volume nor any constant increase in relative plasma volume by the hematocrit was demonstrated. Clinical evidence of edema was absent in the animals studied. It was shown that neither pituitary extract nor large amounts of water alone were capable of producing this phenomenon. Edema of the brain was suggested but could not be proved. A gradual and marked increase in blood pressure is encountered in water intoxication but the changes in blood pressure did not appear striking enough to account for toxic manifestations. From the standpoint of sudden onset and recovery eclampsia also was proposed as a cause.

One of our patients with diabetes insipidus associated with post-encephalitic Parkinson's disease, who was relieved of the polyuria and polydipsia following total thyroidectomy, was of interest in this connection. After thyroidectomy blood volume studies were made with and without the administration of pituitrin. The whole blood volume of 5,000 c c before the use of pituitrin increased to 6,000 c c after the administration of pituitrin. The patient had no toxic symptoms. This variation in the blood volume was in striking contrast to that noted in the patients with diabetes insipidus of idiopathic origin, who showed very little change or none in the blood volume after pituitrin therapy.

It seems possible that patients with diabetes insipidus secondary to encephalitis have a peculiarity which renders them susceptible to retention of fluids and water intoxication following pituitrin administration. In certain cases of post-encephalitic diabetes insipidus a compulsion thirst may exist despite pituitrin therapy and may lead to inordinate

that normal human urine contains a substance, urogastrone which inhibits gastric secretion on intravenous injections in dogs There was a question whether a correlation existed between the content of urogastrone in the urine and the function of some endocrine glands Kaulbersz and associates studied this problem and found that extracts, urogastrone prepared from the urine of normal dogs inhibited gastric secretion and decreased the acidity of gastric juice Urogastrone made from thyroidectomized dogs exerted nearly the same inhibitory influence as urogastrone procured from normal animals Hypophysectomized dogs with diabetes insipidus did not produce urogastrone in adequate amounts to diminish gastric secretion as in the case with urogastrone from normal dogs On the contrary, urine extracts of such animals increased the quantity and the acidity of the gastric juice secreted after histamine injection A statistical analysis of their data supported the conclusion that the pituitary gland plays a role in the formation or excretion of urogastrone

Marañon and associates[31] also called attention to the frequency of acute abdominal syndromes in seven patients suffering from hypophyseal insufficiency including diabetes insipidus These symptoms were classified into two groups One included intestinal paralysis which simulated ileus paralyticus The second group consisted of those with predominance of spasm and pain which stimulated acute appendicitis, perforated peptic ulcer, cholecystitis or some other acute abdominal condition The differential diagnosis is important because the lack of a proper diagnosis may result in unnecessary surgery

Water Intoxication in Patients with Diabetes Insipidus—The phenomenon of water intoxication may appear in patients with diabetes insipidus under certain conditions A patient of Weir and associates[3] continued after the administration of pituitary extract to drink his customary amounts of water and during a period of eight hours he ingested 5 25 liters and excreted only 800 c c of urine In the course of 3 or 4 hours he became acutely ill developed a severe headache and nausea and was forced to go to bed because of water intoxication Physical examination revealed only puffiness of the lower eyelids and slight edema of the ankles Repetition of this procedure on the same as well as on another patient produced the same symptoms as well as ataxia in one case

Snell[39] had similar experiences in three patients with diabetes insipidus of postencephalitic origin who had a daily fluid intake and output of -5 liters when untreated After the administration of pituitrin the

old patient is having some dimness in her vision due to early opacity in the lenses

Mouth —The mouth teeth and saliva were described in the previous section in connection with symptoms of diabetes insipidus The mucous membranes of the mouth usually are dry

Lymph Nodes —The lymph nodes ordinarily are normal General lymphadenitis may occur in cases with leukemia Hodgkin s disease syphilis and other infections

Heart and Blood Pressure —The heart and blood pressure in patients with diabetes insipidus usually are normal Vascular disease is comparatively rare in these individuals X ray of the heart in untreated patients show normal measurements and configuration No changes in these findings were noted after the administration of pituitary extract

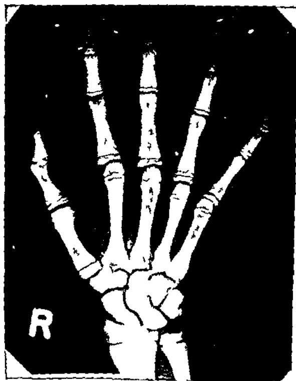


Fig 1 X ray of right hand of an 18 year old boy who has had diabetes insipidus since the age of 5 years It shows that the epiphyses are open and 2 to 3 years behind in development X ray at age of 21 showed epiphyses closed

consumption of water and water intoxication In such instances it is necessary to curb the excessive intake of fluids during pituitrin therapy

Physical Examination

In my experience the general physical condition of the patient with diabetes insipidus of idiopathic origin is normal unless there is some complicating factor When the disease is due to causes such as brain tumor the physical condition depends on the etiological factor On the whole it is fair to say that diabetes insipidus has no appreciable effect on the physical state of these individuals even though the disease has been present for many years Frequently there is an impression that patients with diabetes insipidus have an abnormal appearance This idea stems from the fact that pictures are published not of the normal looking cases but of the rare cases of diabetes insipidus with some complicating disease like Frohlich s syndrome xanthomatosis stunted growth or renal dwarfism Patients with uncomplicated diabetes insipidus have a normal physiognomy

Height and Weight—In general there was no appreciable change from the normal of the height and weight of my patients with diabetes insipidus A few people were fat and a few thin However a rare case with complicating endocrine disturbance was either underdeveloped or short One patient was taller than normal, his height was 6 feet inches

Skin—The dryness of the skin in the past considered a regular symptom of this disease, has been practically absent in our cases The skin and perspiration were normal I have not seen any cases with ichthyosis or eczema Forssman[21], too found no abnormalities with regard to the moisture of the skin or any diminished secretion of sweat

Eyes—The eyes are normal unless the diabetes insipidus is due to a brain tumor, xanthomatosis or syphilis diabetes insipidus in itself causes no eye abnormalities I recall the wearing of glasses by only two patients with diabetes insipidus of idiopathic origin Exophthalmos often is associated with brain tumor and xanthomatosis The cases with brain tumor usually develop loss of vision hemianopsia, constriction of the visual fields diplopia and atrophy of the optic nerve There may be choked disc or optic neuritis Unequal or fixed pupils may be noted in syphilis Cataracts so common in persons with diabetes mellitus were absent in these individuals with diabetes insipidus However, one 82 year

very little change occurred in the red blood count whether or not the patient was on pituitrin On rare occasions the red blood count would decrease by 300 000 or 400 000 or increase by 100 000 or 200 000 following pituitrin therapy Usually the red blood count ranged from approximately 4 500 000 to 5 000 000 If the red blood count was diminished appreciably it was due to some secondary condition such as malignancy bleeding peptic ulcer or deficiency

The *blood smear* showed normal red blood corpuscles with a normal differential of the polymorphonuclear leucocytes lymphocytes and large mononuclear cells

The *sedimentation* rate also appeared within the normal limits in these patients although frequently on the upper side of normal Pituitrin caused no appreciable change in the rate Ichijo[40] found that hypophysectomized dogs in comparison with normal ones showed an increase in the sedimentation rate which was accelerated after pituitrin injection in both types of animals particularly in the hypophysectomized ones

Hematocrit readings were taken in 14 patients with and without pituitrin therapy Illustrations of the results are shown in Table XIV

TABLE XIV

HEMATOCRIT READINGS IN PATIENTS WITH DIABETES INSIPIDUS

Case	Without Pituitrin *Hematocrit* *Corpuscles*	*Plasma*	With Pituitrin *Hematocrit* *Corpuscles*	*Plasma*
	/	/		/
1	41	59	40	60
2	40	60	40	60
3	34	66	36	64
4	4	58	38	62
5	40	60	4	58
6	37	63	34	66
7	45	55	42	58

A number of hematocrits with the percentage of corpuscles as low as 34 or 35 per cent were found with and without pituitrin therapy (see Table XIV) This percentage appeared rather low although the hemoglobin and the red counts appeared normal There has been discussion concerning the dilution of the blood when the patients with diabetes insipidus are placed on pituitrin therapy In our cases variations above and below the original hematocrit readings occurred when the patients were treated with pituitrin but no case revealed any marked dilution or

Lungs—The lungs in patients with diabetes insipidus are normal Respiratory infections are rare in these individuals

Liver, Spleen and Kidneys—The liver, spleen and kidneys usually are normal However, the liver and spleen may be enlarged in leukemia and xanthomatosis

Genitalia—Although genital disturbances have been thought to be quite frequent in these patients, it is uncommon in my experience Hypogenitalism has been present in a few instances particularly when the diabetes insipidus has been due to brain tumor On the other hand there have been rare cases of sexual precocity when the diabetes insipidus occurred simultaneously with pineal gland tumor

Muscles—The muscular system of these individuals usually was normal In cases with postencephalitic Parkinson's disease there was the rigidity which accompanies that syndrome The muscular tone was disturbed in certain cases with tumor

Bones—The examination of the bones of these patients was normal except in the case of retarded growth renal rickets and xanthomatosis In rare instances there was delayed epiphyseal union as observed in an 18-year old boy whose x-rays showed a definite delay in the epiphyseal union of the hand as illustrated in Fig 11

When this boy became 21 years of age another x-ray showed that the epiphysis of the hand had closed However, x-rays of the bones in general are normal unless there is some particular disease causing diabetes insipidus

Central Nervous System—The central nervous system appears normal by examination unless it shows some involvement as a result of tumor or infection In those cases the type of central nervous system findings depends on the location of the tumors and the infection

Laboratory Studies

In our patients with diabetes insipidus many laboratory studies were made on the blood, the blood serum, urine spinal fluid, basal metabolism electroencephalograms and x-rays These observations will be discussed individually

Blood

The *hemoglobin* as well as the red and white blood corpuscular counts in our patients with diabetes insipidus was normal In general

very little change occurred in the red blood count whether or not the patient was on pituitrin On rare occasions the red blood count would decrease by 300 000 or 400 000 or increase by 100,000 or 200 000 following pituitrin therapy Usually the red blood count ranged from approximately 4 500 000 to 5 000 000 If the red blood count was diminished appreciably it was due to some secondary condition such as malignancy bleeding peptic ulcer or deficiency

The *blood smear* showed normal red blood corpuscles with a normal differential of the polymorphonuclear leucocytes lymphocytes and large mononuclear cells

The *sedimentation* rate also appeared within the normal limits in these patients although frequently on the upper side of normal Pituitrin caused no appreciable change in the rate Ichijo[10] found that hypophysectomized dogs in comparison with normal ones showed an increase in the sedimentation rate which was accelerated after pituitrin injection in both types of animals particularly in the hypophysectomized ones

Hematocrit readings were taken in 14 patients with and without pituitrin therapy Illustrations of the results are shown in Table XIV

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HEMATOCRIT READINGS IN PATIENTS WITH DIABETES INSIPIDUS

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Case	*Corpuscles*	*Plasma*	*Corpuscles*	*Plasma*
		/		/
1	41	59	40	60
2	40	60	40	60
3	34	66	36	64
4	42	58	38	62
5	40	60	42	58
6	37	63	34	66
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A number of hematocrits with the percentage of corpuscles as low as 34 or 35 per cent were found with and without pituitrin therapy (see Table XIV) This percentage appeared rather low although the hemoglobin and the red counts appeared normal There has been discussion concerning the dilution of the blood when the patients with diabetes insipidus are placed on pituitrin therapy In our cases variations above and below the original hematocrit readings occurred when the patients were treated with pituitrin but no case revealed any marked dilution or

concentration of the blood A dilution of the hematocrit readings following pituitrin therapy has occurred in rare instances These cases were usually dehydrated when untreated The hematocrit readings coincided or corresponded with those of the blood volume findings

The *whole blood protein* was determined in 14 patients with diabetes insipidus with and without the use of pituitrin The whole blood protein values ranged from 17 3 gm to -5 gm when the patients were treated with pituitrin With the omission of pituitrin the blood protein varied from 18 to -7 gm per c c of blood Illustrations of these results are given in Table XV

TABLE XV

WHOLE BLOOD PROTEIN IN PATIENTS WITH DIABETES INSIPIDUS

Case No	With Pituitrin *Blood gm*	Without Pituitrin *Blood gm*
1	17 3	18 0
2	21 5	0.0
3	24.0	2 .0
4	21.0	19.0
5	5 0	
6	23 0	24.0
7		27 0

There was very little variation in the whole blood protein whether or not the patient was under treatment with pituitrin

The *serum protein, albumin* and *globulin* were determined in 14 patients with diabetes insipidus who were under treatment with pituitrin and again when the pituitrin had been omitted Illustrations of the results are shown in Table XVI

TABLE XVI

SERUM PROTEIN ALBUMIN AND GLOBULIN IN PATIENTS WITH DIABETES INSIPIDUS

	Without Pituitrin			With Pituitrin		
Case	*Protein gm*	*Albumin gm*	*Globulin gm /*	*Protein gm*	*Albumin gm /*	*Globulin gm /*
1	6 8	4 6		6 5	4 2	2 3
2	5 8	3 8	.0	6	4 1	2 1
3	5 2	3 2	2.0	6 1	3 5	2.6
4	5 5	3.9	1.6	6 3	3 5	2.8
5	7 7	5.4	3	6 5	3 8	2 7
6	6 3	4 0	2 3	6 2	3.8	2.4

Several of these serum protein levels were on the low side of normal It was rather interesting to find that the serum protein levels were hardly influenced by pituitrin administration The albumin globulin ratios were normal and fitted in with the total serum protein On the other hand pitressin therapy[36] has been found by others to reduce the serum protein concentration Kourilsky and Fournier[1] reported hyperproteinemia and hyperchloremia which were exaggerated during the restriction of fluid intake in untreated cases of diabetes insipidus

Other Blood Findings

In many patients with diabetes insipidus a normal concentration of the following substances in the fasting blood was found urea nitrogen non protein nitrogen sugar chloride phosphorus alcohol uric acid creatinine magnesium and icteric index In some cases abnormal levels of calcium cholesterol and iodine in the blood were obtained A more detailed discussion of some of these constituents as well as certain tolerance and excretion studies will be presented now

Blood Magnesium — The blood magnesium investigated in two cases with diabetes insipidus was normal In one case the level was 2 3 mgm per 100 c c with and without pituitrin therapy In the second case the magnesium level was 2 mgm per cent when untreated and 2 5 mgm per cent during pituitrin therapy

Serum Calcium and Phosphorus — The serum calcium and phosphorus were determined in 14 patients with diabetes insipidus who were not treated with pituitrin In five of these cases the serum calcium was higher than normal the level being 11 4 to 14 4 mgm per 100 c c The phosphorus in these cases however appeared within the normal range When the patients were treated with pituitrin the serum calcium did not vary appreciably In one case the serum calcium was 11 mgm without pituitrin and 12 8 mgm on pituitrin

Serum Potassium — The fasting serum potassium values were within the normal limits ranging from 4 0 to 4 4 milliequivalents per liter (461) when not receiving pituitrin

Blood Volume

The blood volume was determined in five patients with diabetes insipidus in order to find their normal values and to note any possible

dilution in the blood volume following the injection of pituitrin. The total blood plasma and corpuscular volumes were determined first according to the dye method of Rowntree and associates[41], except that congo red was used instead of vital red and later according to the method of Gibson and Evans[1]. In two cases both methods produced practically identical results. In addition the values in a sixth case observed by Fischer and Beck[213] are included.

The findings are shown in Table XVII and appeared normal for the age, sex and weight of these patients when not treated with pituitrin.

TABLE XVII

THE PLASMA, CORPUSCULAR AND TOTAL BLOOD VOLUMES IN PATIENTS WITH DIABETES INSIPIDUS

Without Pituitrin

Case	*Hematocrit Corpuscles* %	*Corpuscular Volume* c.c.	*Plasma Volume* c.c.	*Whole Blood Volume* c.c.
1	44	1900	2450	4350
2	39	1854	2900	4754
3	41.9	1781	2469	4 50
4	34	1185	2300	3485
5	43	1187	1573	2760
6	45	1765	2160	3925
	4	1745	2410	4155

With Pituitrin

Case	*Hematocrit Corpuscles*	*Corpuscular Volume* c.c.	*Plasma Volume* c.c.	*Whole Blood Volume* c.c.
1	41	1905	2715	46 0
2	40	1866	2800	4666
3	41.3	1900	2,00	4600
4	34	1160	2300	3460
5				
6	43	1840	2445	4 85

There was very little variation in the plasma volume, corpuscular volume and the total blood volume when the patients were treated with pituitrin. In two cases the plasma volume increased by 231 and 265 c.c., when pituitrin was administered, whereas in another there was no change in the plasma volume and a fourth showed a decrease of 100 c.c. in the plasma volume following pituitrin therapy. In a fifth case, that of a boy

aged 11, the blood volume was obtained without pituitrin therapy and here, too results appeared normal In the sixth case there was an increase of 255 c c in plasma volume after pituitrin therapy was started This level remained practically the same when pituitrin was omitted

The means of regulation under ordinary conditions are adequate to maintain a certain constant balance between blood volume and the large volume of tissue water The drinking of water even in large amounts does not alter the balance permanently or appreciably since the excess of water is excreted promptly by the kidneys In diabetes insipidus water is eliminated in an uncontrolled manner from the blood and tissues and the deficit is compensated for by the ingestion of correspondingly large amounts of fluids It is remarkable how constant the blood volumes remain even under these conditions

Results similar to ours have been noted by other investigators Weir Larson and Rowntree [2] carried out blood volume determinations in four patients with diabetes insipidus before and after the administration of pituitary extract For example in one of their cases prior to the administration of pituitary extract the plasma and total blood volumes were 3,460 and 4 805 c c respectively and after the drug 3 495 and 4 855 c c respectively These authors concluded therefore that pituitary extract can control the polyuria of diabetes insipidus and prevent polyuria following excessive ingestion of water without the development of any significant increase in blood or plasma volume These findings are in keeping with the experimental results which they obtained in animals

The data of Talbott and associates[211] who made blood volume determinations in a patient with diabetes insipidus associated with diabetes mellitus are in agreement They noted only small changes in body fluid volumes following abstinence from fluids or ingestion of sodium chloride although thirst was intense Soule [15] also found no significant variations in the blood volume with and without pituitrin therapy in a case of diabetes during pregnancy However it has been shown[3, 4] that pitressin therapy increased the extracellular and plasma volume and reduced the serum protein and hematocrit in diabetes insipidus

Effect of Dextrose and Saline on Blood Volume in Diabetes Insipidus — Plasma volume determinations with the dye T-18 4 have been performed by Fischer and Beck[213] to ascertain certain effects of an intravenous crystalloid solution in diabetes insipidus

In an untreated 47 year old housewife with severe diabetes insipidus 1 000 c c of 5 per cent dextrose in 0 9 per cent saline were injected

dilution in the blood volume following the injection of pituitrin The total blood plasma and corpuscular volumes were determined first according to the dye method of Rowntree and associates[11], except that congo red was used instead of vital red, and later according to the method of Gibson and Evans[1] In two cases both methods produced practically identical results In addition the values in a sixth case observed by Fischer and Beck[213] are included

The findings are shown in Table XVII and appeared normal for the age, sex and weight of these patients when not treated with pituitrin

TABLE XVII

THE PLASMA CORPUSCULAR AND TOTAL BLOOD VOLUMES IN PATIENTS WITH DIABETES INSIPIDUS

Without Pituitrin

Case	*Hematocrit Corpuscles* %	*Corpuscular Volume* c c	*Plasma Volume* c c	*Whole Blood Volume* c c
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6	45	1765	2160	3925
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With Pituitrin

Case	*Hematocrit Corpuscles*	*Corpuscular Volume* c c	*Plasma Volume* c c	*Whole Blood Volume* c c
1	41	1905	2515	46 0
2	40	1866	2800	4666
3	41 3	1900	2500	4600
4	34	1160	2300	3460
5				
6	43	1840	2445	4 85

There was very little variation in the plasma volume, corpuscular volume and the total blood volume when the patients were treated with pituitrin In two cases the plasma volume increased by 231 and 265 c c when pituitrin was administered whereas in another there was no change in the plasma volume and a fourth showed a decrease of 100 c c in the plasma volume following pituitrin therapy In a fifth case, that of a boy

In patients calcium gluconate was injected instead of decholin. The circulation time was normal, being 18 and 19 seconds and 15 and 1 seconds. These results were slightly greater because the end point is not so distinct as with decholin.

Glucose Tolerance Tests

I have determined the fasting blood sugar in many cases of diabetes insipidus and have found it to range from 58 mgm. to 107 mgm. per cent. In a number of patients with diabetes insipidus standard glucose tolerance tests were performed in which 100 gm. of glucose were taken orally after an overnight fast. The blood sugar was determined by the method of Folin and Wu on specimens taken fasting and at intervals of one half, one, two and three hours after the ingestion of the glucose.

In general four types of sugar tolerance curves were encountered in patients with diabetes insipidus. These curves are shown in Fig. 1

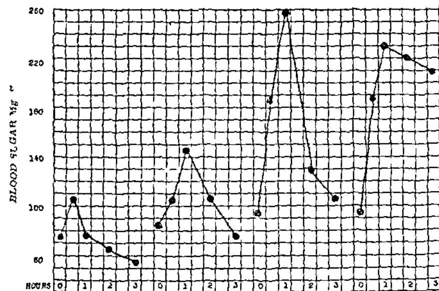


Fig 12 Types of glucose tolerance curves in patients with diabetes insipidus of idiopathic origin after ingestion of 100 gm of glucose. Figures at left represent mgm % of glucose.

intravenously at a constant rate of 7 c c per minute for 140 minutes The plasma volume was determined immediately before and at the end of the injection of this solution Before the injection of the solution the plasma volume was found to be 410 c c with a hematocrit of 4 per cent corpuscles The plasma volume determined again at the end of the injections of the solution was found to be identical with that obtained immediately preceding the injection of the dextrose in saline This solution produced diuresis in the patient

In contrast Fischer and Bowman[256] had made the same studies in a group of convalescent hospital patients who had normal blood volumes and cardio-vascular renal systems After the injection of the glucose saline solution they found that the plasma volume increased from 7 to 37 per cent an average increase of 21 5 per cent and that no diuresis occurred

In summary in a case of diabetes insipidus the intravenous injection of 1 000 c c of 5 per cent dextrose in 0 9 per cent saline at a rate of 7 c c per minute caused no change in the plasma volume and induced some diuresis These findings were in contrast to the results obtained in normal convalescent hospital patients who, under the same conditions showed an average increase of 21 5 per cent in the plasma volume and no diuresis The reason that the patient with diabetes insipidus did not respond to intravenous dextrose in saline as the normal individuals did is questionable Possibly there is an inability to retain the sodium ion which goes out through the kidneys along with the water On the other hand this phenomenon may be explained according to Verney's theories on osmoreceptors The patient with diabetes insipidus may not have osmoreceptors that respond to hypertonic solutions and stimulate posterior pituitary secretion to inhibit diuresis like the normal

Circulation Time

The circulation time was studied by the decholin method in a group of patients with diabetes insipidus with and without pituitrin therapy The test was performed by injecting decholin into the antecubital vein and then the time was noted when the patients obtained a bitter taste In this group of patients the circulation time was normal and ranged from 8 to 12 seconds These findings did not show appreciable changes whether or not the patient was treated with pituitrin

In patients calcium gluconate was injected instead of decholin The circulation time was normal being 18 and 19 seconds and [illegible] and [illegible] seconds These results were slightly greater because the end point is not so distinct as with decholin

Glucose Tolerance Tests

I have determined the fasting blood sugar in many cases of diabetes insipidus and have found it to range from 56 mgm to 107 mgm per cent In a number of patients with diabetes insipidus standard glucose tolerance tests were performed in which 100 gm of glucose were taken orally after an overnight fast The blood sugar was determined by the method of Folin and Wu[24] on specimens taken fasting and at intervals of one half one two and three hours after the ingestion of the glucose

In general four types of sugar tolerance curves were encountered in patients with diabetes insipidus These curves are shown in Fig 12

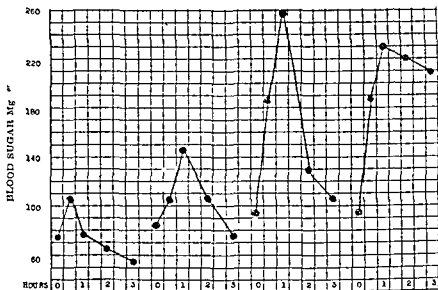


Fig 12 Types of glucose tolerance curves in patients with diabetes insipidus of idiopathic origin after ingestion of 100 gm of glucose Figures at left represent mgm % of glucose

In the first type the fasting blood sugar was normal The blood sugar rose very little and then dropped to a comparatively low level at the end of two or three hours after the ingestion of the glucose This was a rather flat type of sugar tolerance curve

The second type of curve had a normal fasting blood sugar and a normal response following the ingestion of 100 gm of glucose the same is that found in the typical normal person In these cases there was no glycosuria

In the third type of glucose tolerance there was a normal fasting blood sugar and a rather sharp rise in the blood sugar following the ingestion of the glucose to hyperglycemic levels of about 200 to 350 mgm per cent Then a sharp drop to the normal level occurred in two or three hours after the ingestion of the glucose

The fourth type of glucose tolerance had a normal fasting blood sugar level which rose sharply during the glucose tolerance test to an abnormally high level and remained at a high level or dropped very slightly two or three hours after glucose ingestion In the third and fourth types there appeared to be a high threshold for glucose because very little or no sugar was found in the urine in spite of high blood sugar values

The high renal threshold for sugar which has been noted in diabetes insipidus is interesting Possibly these cases may have an appreciable amount of the so called non glucose reducing substance in the figures for the blood sugar as has been pointed out recently in various cases [48, 249] Consequently, very little or no glucose would be found in the urine

Sugar tolerance tests repeated when the diabetes insipidus was controlled with pituitary extract gave results which did not differ appreciably from those obtained in the untreated patients Gibson and associates[50] studied the sugar tolerance in six subjects with diabetes insipidus and found that five of them had a glucose tolerance curve of the type noted in diabetes mellitus but with a high renal threshold for glucose They also observed that the curves were not influenced persistently when the polyuria was controlled with pituitrin

On the other hand John [51] obtained low or normal curves in a series of glucose tolerance tests in two patients with diabetes insipidus Furthermore Lawrence and Hewlitt[2] observed rather flat curves in glucose tolerance tests with blood sugar determinations on both arterial and venous samples on a young man with diabetes insipidus

The cause for the variable types of sugar tolerance tests obtained in

diabetes insipidus is questionable The results showing normal or flat sugar tolerance curves in diabetes insipidus could be explained by the fact that in diabetes insipidus there is a lack of secretion of the posterior lobe of the pituitary gland This idea would be consistent with the results noted by Blotner and Fitz [3] who found that the injection of pituitrin caused a rise in the blood sugar concentration followed by a fall to the normal or below normal Consequently, with the lack of pituitary secretion in diabetes insipidus one would expect the opposite type of a result to that noted following pituitrin injection The explanation of those sugar tolerance curves which are markedly diminished is more difficult Possibly these results could be explained by a marked overactivity of the anterior pituitary gland This may be similar to the relationship of the anterior pituitary gland to diabetes mellitus

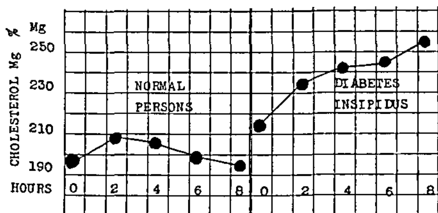


Fig 13 Average plasma cholesterol curves after a test meal of 100 gm of fat in 13 normal persons and in 7 patients with diabetes insipidus

Fat Tolerance Tests

I have found an increased blood cholesterol concentration in a number of cases with diabetes insipidus and in obese patients This rise it appeared might be due to a deficiency of the posterior lobe of the pituitary gland Consequently this problem[254] was investigated further by studying the blood fat tolerance in patients with diabetes insipidus In addition the effect of the administration of pituitrin pitocin pitressin and antuitrin on these tests was determined

In the first type the fasting blood sugar was normal. The blood sugar rose very little and then dropped to a comparatively low level at the end of two or three hours after the ingestion of the glucose. This was a rather flat type of sugar tolerance curve.

The second type of curve had a normal fasting blood sugar and a normal response following the ingestion of 100 gm. of glucose, the same as that found in the typical normal person. In these cases there was no glycosuria.

In the third type of glucose tolerance there was a normal fasting blood sugar and a rather sharp rise in the blood sugar following the ingestion of the glucose to hyperglycemic levels of about 200 to 350 mgm. per cent. Then a sharp drop to the normal level occurred in two or three hours after the ingestion of the glucose.

The fourth type of glucose tolerance had a normal fasting blood sugar level which rose sharply during the glucose tolerance test to an abnormally high level and remained at a high level or dropped very slightly two or three hours after glucose ingestion. In the third and fourth types there appeared to be a high threshold for glucose because very little or no sugar was found in the urine in spite of high blood sugar values.

The high renal threshold for sugar which has been noted in diabetes insipidus is interesting. Possibly these cases may have an appreciable amount of the so-called non glucose reducing substance in the figures for the blood sugar as has been pointed out recently in various cases.[48, 249] Consequently, very little or no glucose would be found in the urine.

Sugar tolerance tests repeated when the diabetes insipidus was controlled with pituitary extract give results which did not differ appreciably from those obtained in the untreated patients. Gibson and associates[50] studied the sugar tolerance in six subjects with diabetes insipidus and found that five of them had a glucose tolerance curve of the type noted in diabetes mellitus but with a high renal threshold for glucose. They also observed that the curves were not influenced persistently when the polyuria was controlled with pituitrin.

On the other hand John[51] obtained low or normal curves in a series of glucose tolerance tests in two patients with diabetes insipidus. Furthermore, Lawrence and Hewlitt[52] observed rather flat curves in glucose tolerance tests with blood sugar determinations on both arterial and venous samples on a young man with diabetes insipidus.

The cause for the variable types of sugar tolerance tests obtained in

13 normal persons as control tests An illustration of the results are given in Fig 13 There was variation in the plasma cholesterol level after the patients had fasted but comparatively little change as the result of the fat meal The striking feature in normal people is the flatness of the cholesterol curve following the ingestion of a fat meal Others [7,25] have reported the same findings in normal people

Diabetes Insipidus — The fat tolerance was studied in seven patients with diabetes insipidus and the results are shown in Table XVIII

Without extract of pituitary there was a marked elevation of the plasma cholesterol concentration following the ingestion of cream similar to that in obese subjects In cases 1 2 and 5 the cholesterol level continued to rise during the entire eight hour period of observation In no case did the cholesterol curve appear to depend on the patient's state

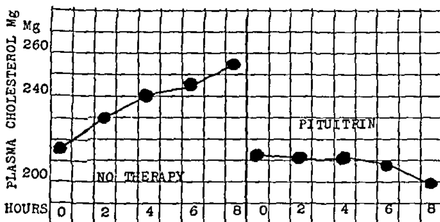


Fig 14 Plasma cholesterol curves obtained after test meal of 100 gm fat in 7 patients with diabetes insipidus with and without pituitary extract administration

of nutrition because some of the patients were thin and none remarkably fat When extract of pituitary was administered after the ingestion of cream and at two-hour intervals subsequently the plasma cholesterol level was flattened showing a normal type of reaction as illustrated in Fig 14

The effect of the oxytocic and pressor principles of the posterior lobe of the pituitary was determined by using pitocin and pitressin It was found that the action of pitressin and pitocin resembled that of pituitrin

The fat tolerance was studied by giving to the patients in the morning after they had fasted overnight 100 gm of fat in the form of 500 c c of 20 per cent cream as a test meal The cholesterol was used as an indicator of the concentration of blood fat because its percentage varies with the total amount of blood fat [5] The cholesterol was determined[56] in samples of blood obtained after the individuals had fasted and two four six and eight hours after the fat meal was ingested The tests were

TABLE XVIII

FAT TOLERANCE IN PATIENTS WITH DIABETES INSIPIDUS

Plasma Cholesterol Levels mgm per 100 c.c of Blood Plasma

No Pituitary Administered

Hours After Test Meal

Case	Fasting	2	4	6	8
1	256	289	308	318	358
2	40	249	63	71	297
3	187	195	223	234	231
4	187	195	05	15	199
5	201	215	25	228	237
6	201	13	234	228	225
7	234	57	20	225	228
Average	215	240	40	46	254

Pituitary Administered

Hours After Test Meal

Case	Fasting	2	4	6	8
1	38	50	264	64	240
2	240	43	243	253	240
3	180	189	185	168	171
4	187	183	180	185	191
5	208	201	205	197	187
6	195	201	205	191	191
7	234	08	05	01	166
Average	212	211	212	208	198

Extract of pituitary was administered intranasally immediately after each specimen of blood was taken

This consisted of 500 c c of 0 per cent cream

made on one day without pituitrin, pitocin or pitressin and later after several days after the administration of these drugs They were given intranasally on a pledget of cotton in one c c doses on different days immediately after the ingestion of the cream and every two hours just after the specimens of blood were taken

Normal Persons — Fat tolerance tests were obtained in a group of

13 normal persons as control tests An illustration of the results are given in Fig 13 There was variation in the plasma cholesterol level after the patients had fasted but comparatively little change as the result of the fat meal The striking feature in normal people is the flatness of the cholesterol curve following the ingestion of a fat meal Others[3 -4] have reported the same findings in normal people

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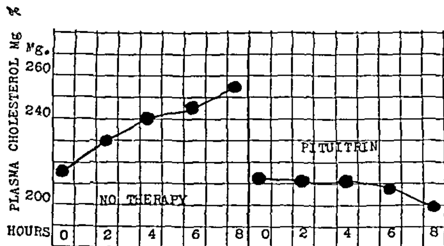


Fig 14 Plasma cholesterol curves obtained after test meal of 100 gm fat in 7 patients with diabetes insipidus with and without pituitary extract administration

of nutrition because some of the patients were thin and none remarkably fat When extract of pituitary was administered after the ingestion of cream and at two hour intervals subsequently, the plasma cholesterol level was flattened showing a normal type of reaction as illustrated in Fig 14

The effect of the oxytocic and pressor principles of the posterior lobe of the pituitary was determined by using pitocin and pitressin It was found that the action of pitressin and pitocin resembled that of pituitrin

While there was a marked rise in the plasma cholesterol level in individuals with diabetes insipidus after a fat meal, comparatively little variation was encountered in the plasma cholesterol concentration after the administration of pitressin or pitocin. However, pitressin appeared to have a somewhat greater effect than pitocin, which in one case did not prevent the rise in the blood cholesterol level.

Antuitrin. — Anselmino and Hoffman[59], as well as others[60], have shown that a special fat metabolism hormone can be extracted from the anterior lobe of the pituitary body, the presence of which causes a rise in the acetone bodies of the blood. On the other hand Munoz[61] and Evans[6] have demonstrated respectively that the injection of extract of the anterior lobe of the hypophysis causes an increase in the blood cholesterol and marked lipemia in dogs. Since the extract of the anterior lobe of the pituitary is said to contain a fat hormone, its effect also was checked on fat metabolism in two patients with diabetes insipidus by using the fat tolerance tests. Antuitrin, the soluble extract of the anterior lobe of the pituitary, was injected subcutaneously in 1 c c doses immediately after the ingestion of the cream and every two hours just after the specimens of blood were taken. Incidentally, the effect of antuitrin 'S', the anterior pituitary like sex hormone obtained from the urine of pregnancy, was tested also in 1 c c doses in the same manner. The administration of antuitrin and antuitrin 'S' did not cause any significant change in the plasma cholesterol level in these patients, the cholesterol curves remaining much the same as in the control tests. If the antuitrin contains a fat metabolism hormone, it is not evident according to the results obtained with these fat tolerance tests.

These data show that there is an increase in the blood cholesterol in diabetes insipidus after a fat meal and that extracts of pituitary modify appreciably the type of blood fat curves obtained after a fat meal causing a fall in blood fat concentration. Possibly the pituitary dysfunction in diabetes insipidus allows an increase in the blood cholesterol which is brought to normal when certain pituitary extracts are administered. These findings may be accounted for in part by the marked increase in the fatty acids which Coope and Chamberlain[63] found to be deposited in the liver of animals following the administration of pituitary extract. It appears that there is some substance common to pitressin and pitocin and present in pituitary extract which acts on fat metabolism. However, the available solutions of pitocin and pitressin are not entirely free of each other.

Urine

In untreated cases of diabetes insipidus the urine is normal except for a persistently low specific gravity of about 1 000 or 1 003 A specific gravity of 1 010 or more makes the diagnosis of diabetes insipidus unlikely If the fluid intake is restricted the specific gravity may rise to approximately 1 01 This is also true during fever The color is watery and the reaction usually is neutral The daily volume in most cases is approximately 10 liters and in unusually rare instances as much as 40 liters The urine contains no albumin or sugar and no other abnormal elements unless there is some complicating condition There is ordinarily no sediment On the contrary in cases of diabetes insipidus treated with posterior pituitary extract the urine becomes concentrated and assumes an amber color The specific gravity rises to about 1 0 0 and the urine volume drops to a normal quantity of about 000 c c daily

Blood and Urine Chlorides and Iodine

In addition to the preceding studies I have made observations on the chlorides iodine and alcohol in the urine as well as the blood in patients with diabetes insipidus

Blood and Urine Chlorides in Diabetes Insipidus — The polyuria of diabetes insipidus may be regarded as a diuresis and one would expect to find an increased excretion of sodium chloride in the urine and a decreased serum chloride concentration since diuretics cause an increased excretion of salt along with the increased volume of urine There are differences of opinion with regard to these phenomena because some investigators have reported the occurrence of hyperchloremia and hypochloremia as well as hyperchloruria and hypochloruria in diabetes insipidus Different results too have been found on the effect of pituitrin on the serum and urine chlorides in this disease Such variable impressions have been based largely on rare cases

There has been considerable interest in chlorides in relation to diabetes insipidus for many years As far back as 187 Neubauer and Vogel[11] and Oppenheim[8] found the enormous amount of 0 to 30 gm of sodium chloride in the daily urine of five cases of diabetes insipidus There was a marked salt hunger and when the salt intake was reduced the sodium chloride excretion was less although the urine volume was unchanged The salt had no diuretic effect More recently however it

has been shown[66, 67] that the output of sodium chloride in diabetes insipidus was normal but increasing the salt in the diet increased the total volume of urine in order to eliminate the excess salt Curtis[68] also observed that under water restriction with salt feeding the kidneys were able to concentrate both chlorides and solids Swan[69] suggested that the changes in water metabolism in diabetes insipidus are secondary to those in chloride metabolism Peters[70] reported that small amounts of salt are swept out by the flow of water On the other hand Weil[71] obtained varying results with serum and urine chlorides in four cases and classified diabetes insipidus into the hyperchloremic-hypochloruric and hypochloremic-hyperchloruric types

Hyperchloremia in untreated diabetes insipidus also has been reported[41, 68] Some authors have found that blood chlorides decreased following pituitrin administration[36] It has been observed[73] that pituitrin stimulated and increased the total chloride excretion in the urine while the diabetes insipidus was relieved

In contrast there have been studies in treated and untreated cases with this disease which indicated that the blood chloride concentration was normal[4, 5, 76] or low and that the excretion of salt was not affected or was decreased by pituitrin administration In addition White and Findley[8] and Smith and MacKay[8] noted that pituitrin did not affect the total urine chloride excretion while Weir[75] observed a distinct drop in it Mainzer[9] found that a very low serum chloride in untreated cases of diabetes insipidus rose to normal after pituitrin therapy

I[80] studied the chloride content of the serum and urine in 22 patients with diabetes insipidus with and without pituitary extract therapy The patients studied were ambulatory and had had diabetes insipidus for a number of years Their salt intake appeared to be normal and they had no craving for it The diets were the same during the various tests Most of the patients had a daily urine output of about 10 liters without treatment and responded to pituitrin therapy

The serum chloride was determined on one or more occasions in these patients without the administration of pituitrin and the fluids were taken as desired usually ranging from 8 to 14 liters daily The serum chloride was tested again after the patients were well controlled with pituitrin therapy and the fluid intake was within the normal range

The results of the serum chloride findings were consistent and did not show the variations recorded by observers already mentioned The chloride concentrations in all instances came within the normal range regardless of whether the patient had omitted pituitrin for only a few

days or whether he had not been treated with pituitrin for several years and excreted gallons of urine daily during the period However in two cases the serum chloride may be considered slightly elevated being 41 and 421 mgm per 100 c c serum The administration of pituitrin did not alter the results appreciably because the serum chloride concentrations were only a few milligrams above or below those levels when no pituitrin was taken The diuretic effect of the diabetes insipidus and the antidiuretic of pituitrin did not affect the serum chlorides in these cases Illustrations of the results are shown in Table XIX and Table XX

TABLE XIX

SERUM CHLORIDE IN PATIENTS WITH DIABETES INSIPIDUS WITH AND WITHOUT PITUITRIN ADMINISTRATION

Case No	No Pituitrin Serum Chloride mgm per 100 cc	On Pituitrin Serum Chloride mgm per 100 cc
1	388	394
2	349	335
3	34	360
4	364	364
5	412	3 0
6	340	358
7	364	370
8	3 9	355
9	39	395

TABLE XX

SERUM CHLORIDE IN 7 PATIENTS WITH DIABETES INSIPIDUS WHO HAD NO PITUITRIN FOR A LONG TIME — 2 MONTHS TO SEVERAL YEARS

Case No	Serum Chloride mg per 100 cc	Daily Fluid Intake Liters	Period Without Pituitrin
1	343	10 14	2 months
2	340	8 11	several years
3	347	10	several years
4	357	7 10	several years
5	44	-9	1 year
6	358	4 5	1 year
7	375	8 10	6 months

Studies of the total chloride excretion were made in two patients who were on a daily diet of 200 gm of carbohydrate, 90 gm of fat, 90 gm of protein and 10 gm of sodium chloride The urinary chloride is expressed as sodium chloride in the charts so that the excretion of salt may be compared more easily with its intake In the first case the total excretion of chloride in the urine was determined daily for 28 days and

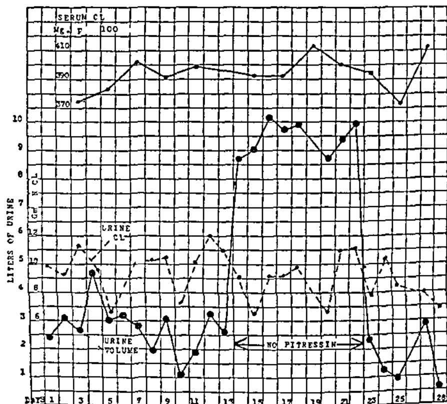


Fig 15 Daily NaCl excretion and urine output and serum chloride in a patient with diabetes insipidus with and without pituitrin therapy Diet was constant and contained exactly 10 gm salt daily Pitressin 1 c c was injected every 6 hours Case 1

the results are shown in Fig 15 With pituitrin therapy the average sodium chloride excretion was 9 7 gm daily the daily range being 6 7 to 12 gm Then when no pituitrin was given the daily average sodium chloride excretion was 9 1 gm with a range of from 6 7 to 11 [illegible] gm Finally when pituitrin was injected again the average sodium chloride excretion was 8 3 gm daily with a range of from 6 8 to 10 4 gm The

serum chloride level showed some slight daily variations whether or not pituitrin was given

This patient was studied a month later to determine the effect of fluid restriction on the blood and urine chlorides When pituitrin was omitted on one day the fluid intake was limited to 3 200 c c and the urine volume was 6 050 c c As a result the patient lost approximately three kilos of weight and developed such a terrific thirst that he was unable to restrict the fluid intake any longer The temperature was unaffected Subsequently he was given fluids as desired without pituitrin These findings illustrated in Fig 16 show that the serum chloride concentra

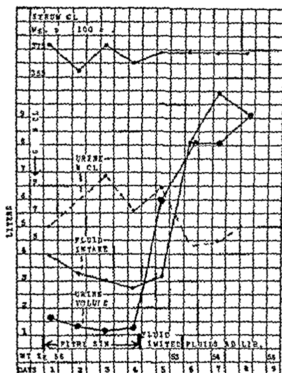


Fig 16 Effect of restricting the fluid intake without pitressin for 1 day on the NaCl excretion and on the serum chloride in Case 1 with diabetes insipidus Diet contained exactly 10 gm salt daily *Pitressin 1 c c was injected every 8 hours*

tion and the excretion of salt in the urine showed no significant variation during the period of observation regardless of the volume of urine This was especially true on the day when the fluid intake was restricted and resulted in a considerable loss of weight

In the second case the total excretion of chloride in the urine was determined for 18 days without pituitrin therapy when the urine volume was about 13 liters, and with pituitrin therapy, when the urine volume was about two liters In this case, too, there were variations in the daily excretion of salt during the different periods of observation with results much like those obtained in the first patient

While not a part of this study of 22 individuals a case of severe diabetes insipidus observed in the hospital some years ago was of unusual interest The patient's daily volume of urine usually ranged from 32,000 to 37 000 c c , although on one day the output rose to about 40,000 c c His total urinary chloride expressed as sodium chloride was found to be 12 1 gm during one 24 hour period when the urine volume was 25,760 c c These figures show that salt is not swept out by the large flow of urine

The results of this investigation were consistent No changes from the normal were found in the serum chloride concentration or in the sodium chloride excretion in the urine in this group of patients The chloride in the spinal fluid of 10 of these patients also has been [81] normal Pituitrin administration did not appear to produce any significant chloride changes in the blood or urine of these patients If anything, this drug decreased the salt excretion These results are in contrast to those which showed in diabetes insipidus abnormal changes in the blood chloride concentration and a diminished salt excretion stimulated by pituitrin administration Even in normal persons Manchester[73] and Smith and MacKay [78] noted that posterior pituitary extracts produced a large increase in the sodium and chloride excretion in the urine

A number of investigators have shown that various diuretics increase markedly the chloride excretion in the urine Among them are Fulton and associates [43] who found in addition, that pituitrin in normal dogs inhibited the increased urine volume after novasural but did not prevent the increased chloride excretion That certain diuretics increase the salt excretion in diabetes insipidus also has been shown Meyer[1] observed in this disease that theocin did not affect the total amount of fluid excreted but it raised the concentration of sodium chloride in the urine so that during the 24 hours after its administration the excretion of salt was increased When theocin was omitted, the chloride output diminished until the normal balance was regained Fitz [66] gave theocin and theobromin sodium salicylate which alone had no diuretic action in this case nor did they increase the total output of sodium chloride However when theocin and salt were given together a larger output of chloride

was obtained than when no theocin was included Lindeboom[41] however obtained a diuretic effect with salyrgan and an unusually high concentration of salt in the urine for this disease although the blood chloride concentration showed no significant changes From my experiments it appears that the diuretic effect of diabetes insipidus and the antidiuretic effect of pituitrin do not alter the total serum and urine chlorides in these patients

These cases show that patients with diabetes insipidus maintain a normal chloride balance when they take an ordinary amount of salt in their diet notwithstanding the exchange of huge volumes of fluid or the administration of pituitrin

Blood and Urine Iodine in Diabetes Insipidus — Our observations[79] on total thyroidectomy indicated that there is a relationship between thyroid activity and water balance in patients with diabetes insipidus It appeared that this association could be established more firmly by observing the levels of iodine in the blood and the excretion of iodine in the urine in a group of patients with diabetes insipidus Consequently I[85] studied the blood and urine iodine in a group of 15 patients with diabetes insipidus

Iodine is a normal constituent of human blood and urine In persons without clinical evidence of thyrotoxicosis[86 8] the average level of iodine in the blood is 6 8 micrograms per 100 gm Curtis and Puppel[8] reported that the normal person excreted in the 24 hour daily urine from 007 to 196 mgm of iodine or an average of 051 mgm whereas in Boston Perkin found the daily urine excretion of iodine to range from 060 to 140 mgm with mean values of 090 to 110 mgm However minor variations of the blood iodine level may occur physiologically[87 88 89 90 93] as well as in certain diseases[89 91] The greatest variation from the normal appears in patients with hyperthyroidism in whom Perkin and Lahey[88] found the average and mean values for blood iodine to be 15 5 and 11 micrograms per 100 gm respectively and the urinary iodine excretion[8] to average 110 to 225 mgm per 24 hours with a maximum of 410 mgm Curtis and Puppel[86] observed a daily excretion of iodine in the urine ranging from 013 to 9 54 mgm with averages ranging from 030 to 595 mgm in hyperthyroidism

The total iodine with its organic and inorganic fractions in the blood and the iodine in urine were determined during and after a course of pituitrin therapy in 15 of our cases with diabetes insipidus In addition other iodine studies were made The tests for iodine in the urine were made on 24 hour samples of urine obtained immediately before or after

the blood was taken. The patients did not have a sea fish meal which might reflect an increased amount of iodine in the blood and urine.

A summary of the results of the total blood iodine levels and of the total iodine excretion in the 24 hour daily urine in 12 cases of idiopathic origin is given in Table XXI.

TABLE XXI

TOTAL IODINE IN BLOOD AND URINE IN 12 PATIENTS WITH DIABETES INSIPIDUS

	Blood Iodine mcg per 100 cc	*24 hour urine iodine mgm*	*24 hour urine volume cc*
	No Pituitrin		
Average	5.8	319	9460
Range	3.0-12.6	.08 936	
	On Pituitrin		
Average	9.4	189	2.860
Range	4.2 17.8	.078 .466	

These findings show that when no pituitrin was administered the blood iodine usually was at a low normal level although in one specimen it was elevated being 12.6 micrograms per 100 c.c. The average was 5.8 micrograms per 100 c.c. in comparison with the average blood iodine of 6.8 micrograms in normal people.

The 24 hour urine showed varying amounts of iodine and in most instances the iodine excretion was markedly increased. The average 24 hour urine iodine was 319 mgm. with an average daily urine volume of approximately 10 liters.

Pituitrin administration produced results opposite to those obtained when the drug was not given. In this instance the blood iodine level was increased in most cases and the 24 hour urine excretion of iodine was decreased considerably. The average blood iodine was 9.4 micrograms per 100 c.c. and the average daily urine iodine was 189 mgm. with an average daily urine volume of approximately three liters.

These findings show that in an untreated case of diabetes *insipidus* there is an increased excretion of iodine in the urine and an associated low normal level of iodine in the blood. When these patients are treated with pituitrin the opposite occurs, the excretion of iodine in the urine is diminished and the blood iodine level is increased.

In two patients with diabetes insipidus relieved of their polyuria and polydipsia following total thyroidectomy the blood iodine levels were

low ranging from 1 5 to 4 8 micrograms per 100 c c and the excretion of iodine in the urine was normal These results are comparable to those obtained in myxedema the average blood iodine level being 3 5 micro grams per 100 c c

One patient was admitted to the hospital for observation for 20 days The iodine was determined daily on fasting samples of blood and on 24 hour specimens of urine The patient was given a house diet which contained about 150 mgm iodine daily The patient took no pituitrin for two weeks before admission to the hospital and her daily urine output approximated 10 liters The results of her iodine studies are given in Fig 17

During the first seven days in the hospital no pituitrin was administered and the patient s urine volume varied from 8 to 13 liters The blood iodine level was at first normal and then decreased to a low level while the urine iodine excretion was at first low and then increased considerably For the next 10 days pituitrin was injected so that the daily urine volume was normal During this period the iodine excretion in the urine decreased and became low while the blood iodine levels increased markedly These blood iodine results were not fortuitous because the organic and inorganic iodine fractions were determined also and they amounted to the total blood iodine concentration However on the last three days of this period the blood iodine dropped to a very low level Finally pituitrin was omitted again for three days and the urine volume ranged from 1 to 14 liters the iodine excretion increased again and the blood iodine remained at a high normal level Incidentally the iodine content of pituitrin was determined and found to contain an insufficient amount of iodine to influence the blood and urine results

The fractionation of the iodine of the blood was carried out in 11 cases [2] in an endeavor to find if the proportion of organic to inorganic iodine in the blood of patients with diabetes insipidus was different from that found in normal individuals and in patients with hyperthyroidism and with myxedema The approximate proportions of organic to inorganic iodine are 65 to 35 in the normal 55 to 45 in hyperthyroidism and 40 to 60 in myxedema The results of this study indicated that the relationship of the organic to inorganic blood iodine was not considered to be abnormal in these cases of diabetes insipidus for their total blood iodine level whether or not pituitrin was administered In a few of the cases the normal relation of the organic and inorganic iodine was reversed The significance of this reversal is not apparent

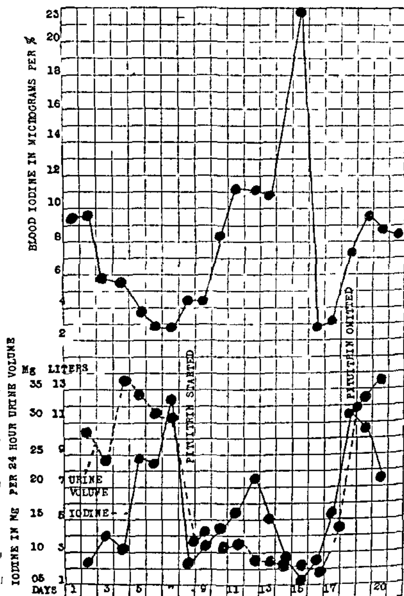


Fig 17 Iodine in blood and urine in a patient with diabetes insipidus with and without pituitrin

Iodine Tolerance Tests — Iodine tolerance tests were made in three cases in order to determine whether the thyroid gland has an extra affinity for iodine similar to the hyperplastic thyroid gland of patients with exophthalmic goiter The concentration of the blood iodine was determined in specimens taken during fasting and at intervals of ½ 1 1½ and 2½ hours after the ingestion of 6 c c of compound solution of iodine (Lugol s solution) U S P In one case the total amount of iodine was determined in the urine excreted during the 24 hours following the ingestion of the iodine The results are given in Table XXII

TABLE XXII

IODINE TOLERANCE TESTS IN 3 PATIENTS WITH DIABETES INSIPIDUS

Case	*Fasting*	*Hours After Iodine Ingestion*				
	0	½	1	1½	2½	
		Blood Iodine mcg				
5	9	275	355	274	26	No Pituitrin
	7	84	57	38	56	On Pituitrin
6	6	93	134	69	109	No Pituitrin
3	6	248	203	165	158	No Pituitrin—48 mg iodine excreted in 24 hours after ingestion of iodine
	7	230	200	163	174	On Pituitrin—25 mg iodine excreted in 4 hours after ingestion of iodine

It has been shown[98, 99] by means of these tests that when a specific amount of iodine is given to persons with hyperthyroidism the iodine in the blood does not rise as high as in normal persons and returns to the basal level more rapidly In contrast when patients with thyroid deficiency are given iodine intravenously the blood iodine rises to higher levels than normal and falls more slowly to the basal level and a greater amount of iodine is recovered in the urine

In case 5 (see Table XXII) when pituitrin was given the blood iodine curve was much lower than normal and like that observed in hyperthyroidism When no pituitrin was administered the blood iodine level was more than twice as high as that found in normal people In case 6 the blood iodine curve was normal without pituitrin In case 3 the blood iodine curves with and without pituitrin were much the same but about twice as high as normal However with pituitrin 25 mgm of iodine were excreted in the urine during the 4 hours after the ingestion

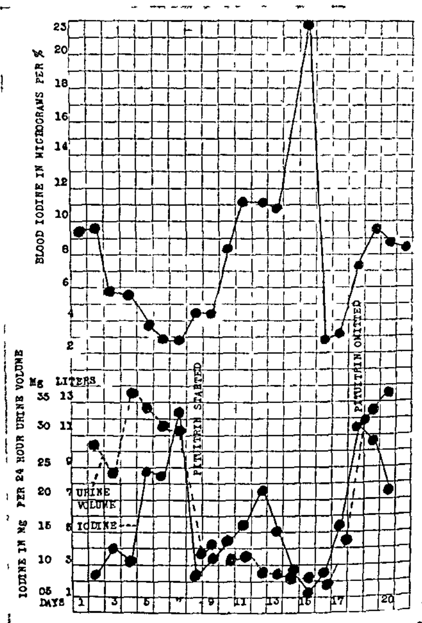


Fig 17 Iodine in blood and urine in a patient with diabetes insipidus with and without pituitrin

50 mgm in one and one half hours and decreased in four hours to an average level of 16 mgm This concentration was appreciably lower than that in the blood at the first half hour but exceeded it at one hour and one and one half hours Also the blood alcohol during its period of decline was slightly lower than the urine alcohol

The alcohol curves obtained in diabetes insipidus without pituitrin therapy were similar to but slightly higher than those observed in normal persons as shown in Fig 18 Pituitrin injection prevented the usual rise in the alcohol concentration in the blood and urine after the alcohol meal as shown in Fig 19 This condition may be due to the inhibiting influence of the pituitrin on the absorption of alcohol or to the fact that

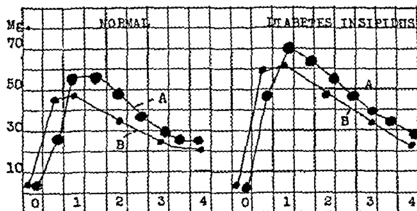


Fig 18 Alcohol curves for (A) urine and (B) blood obtained in 10 normal persons and 5 with diabetes insipidus after the ingestion of 0.6 c.c of absolute alcohol per kg of body weight

in uncontrolled diabetes insipidus the alcohol is not metabolized so quickly as in the controlled disease

It was noted that the blood and urine alcohol levels were higher when the alcohol was taken without pituitrin and when the urine volume was as much as 400 c c per specimen After the administration of pituitrin each specimen of urine usually amounted to only 10 or 20 c c This difference indicates that the kidneys acted like an *inert membrane* and that the alcohol passed through them into the urine by simple diffusion[3, 5, 801] *Consequently the large volume of urine did not dilute its* alcohol content

of iodine as compared with 48 mgm of iodine when no pituitrin was given

The data in this study reveal that in untreated patients with diabetes insipidus there is an increased excretion of iodine in the urine and usually relatively low normal blood iodine levels The most likely cause for these changes is a washing out process resulting from the exchange of large volumes of fluids in these patients and the failure of reabsorption by the kidney, although the possibility of a thyro-pituitary relationship should be considered When pituitrin is administered the blood and urine iodine results are reversed, and the fluid intake and output are markedly decreased, because of the effect of pituitrin which causes increased reabsorption in the kidney This idea may be strengthened by the fact that pituitrin diminishes the excretion of iodine in the urine after the ingestion of Lugol s solution Diodrast clearance tests[300] made in some of these patients also suggest that pituitrin diminishes the excretion of iodine

Alcohol Tolerance Tests

There are very few conditions which are known to modify the rate of absorption or metabolism of alcohol Normal people have a varying tolerance to alcohol just as they do to tobacco and other drugs A few of my patients with diabetes insipidus have stated that they have an unusual tolerance for liquor I[301] have made alcohol tolerance tests in normal persons and in patients with diabetes insipidus The effect of pituitrin and food intake also was determined

The tests were made by giving 0 6 c c of absolute alcohol per kilogram of body weight to the patient after an overnight fast The alcohol concentration was determined by Gibson and Blotner's method[10] on simultaneous samples of venous blood and urine which were obtained before the test meal and at half hour intervals for four hours thereafter The patients took no food during the test period

In 10 normal persons the fasting blood alcohol varied from 0 to 7 mgm per cent After the ingestion of alcohol there was a rise in the curve which reached its average maximum concentration of 41 mgm in one hour and decreased gradually to a level of approximately 15 mgm in four hours as shown in Fig 18

The fasting urine alcohol varied from 0 4 to [illegible] mgm per cent After the ingestion of alcohol it rose to an average maximum concentration of

patients to sleep, one patient, however, showed no special change. All these individuals seemed to experience a more immediate effect of the alcohol without pituitrin. Pituitrin possibly caused the retention of a greater amount of alcohol in the tissues giving intensified alcoholic symptoms. Under such circumstances the blood and urine alcohol might not give a proper indication of the alcohol concentration in those tissues.

Ordinarily the blood and urine alcohol levels are very close because alcohol passes through the kidneys into the urine by a simple process of diffusion. The reason for the slight difference is explained[3] by the fact that the alcohol concentration is slightly higher in arterial than venous blood and consequently gives the slight variation between the alcohol level of the urine and of venous blood.

Some of our patients with diabetes insipidus appear to have an increased tolerance to alcohol. Newmark[30] described a boy in whom an infundibular tumor had caused diabetes insipidus with unusual tolerance of alcohol. The diabetes insipidus began when the patient was nine years old, and he drank two gallons of water during the night. He had smoked since the age of six years and had a propensity to swear dreadfully. He would drink rapidly three to four glasses of beer or a few glasses of wine. Immediately after consuming 4½ quarts of beer without effect he would go to school and do well. He died at the age of 14 years after having brain tumor signs for two weeks before his death.

An attempt was made to produce a condition similar to diabetes insipidus in five normal persons by having them drink large amounts of water during the test period so that they voided large volumes of urine. Several days later the tests were repeated with the administration of 1 c.c. of pitressin when the usual dose of alcohol was ingested and the urine output was small. These tests were compared with those of the controls who received no pituitrin or extra water.

The increased water intake produced a slightly greater concentration of alcohol in the blood and urine during the first one and a half hours after the ingestion of alcohol than occurred during the control tests. It was interesting that the alcohol concentration was not diluted although the volume of urine was increased more than tenfold at times. Miles[31] also found similar results. In contrast, pitressin perceptibly decreased the volume of urine and the alcohol concentration in the blood and urine as it did in diabetes insipidus. Widmark[38], on the other hand, found that pituitrin did not alter the blood alcohol curves in dogs.

It has been known that food in the stomach has an inhibitory action on the symptoms of alcohol intoxication. This effect has been attributed

It was of unusual significance that the toxic effect of alcohol was more marked and more prolonged with pituitrin therapy, even though

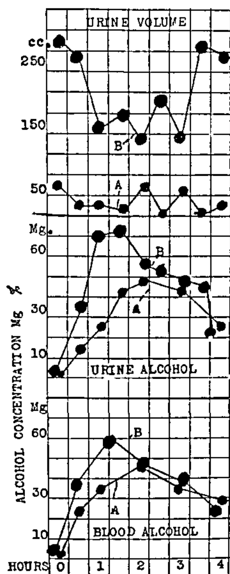


Fig 19 Simultaneous curves showing the blood and urine alcohol levels and the urine volume in a man with diabetes insipidus after the ingestion of 35 c.c of absolute alcohol (A) with and (B) without pituitrin therapy

the blood and urine alcohol levels were lower The toxic symptoms increased so much that pituitrin administered with the alcohol put three

those in the blood serum The chloride and protein contents also were determined Illustrations of the results are shown in Table XXIII

The concentration of the calcium in the cerebrospinal fluid is remarkably constant in health and disease and normally varies from 4 5 to 5 5 mgm[312] The phosphorus content ranges from 1 to 1 5 mgm per 100 c c

The cerebrospinal fluid is regarded by certain investigators as normally a protein free filtrate of the blood plasma and its calcium content is considered to be the diffusible or ionized calcium of the blood or approximately one half of the total blood calcium concentration[313] The other half of the serum Ca is the non diffusible fraction and remains with the protein in the serum However there are certain diseases which may have an increase in the calcium up to 7 5 mgm per 100 c c cerebrospinal fluid particularly meningitic or other fluids with a high protein content[314, 31] and in cases with hydrocephalus and brain tumor[316] and hyperparathyroidism[31]

In our cases with diabetes insipidus the ionized concentration was calculated according to a Cartesian nomogram which McLean and Hastings[316] made for the purpose Control tests were made in 10 patients with syphilis on whom diagnostic lumbar punctures were performed

In the control tests the calcium concentration of the spinal fluid ranged from 3 9 to 5 6 mgm per 100 c c or from 1 to 1 4 mM (millimol) per liter of spinal fluid the average being 1 7 mM per liter The total serum calcium varied from 9 5 to 11 mgm per 100 c c or from 2 58 to 96 mM per liter of water the average being 2 79 mM The ionized Ca concentrations of serum ranged from 1 11 to 1 38 mM per liter of water the average being 1 4 mM The total calcium in the spinal fluid was nearly the same as the ionized Ca concentration of the serum the average difference being + 03 mM per liter which corresponds with the results obtained by McLean and Hastings

In the patients with diabetes insipidus the results were somewhat different The total calcium in the spinal fluid ranged from 4 to 7 4 mgm per 100 c c or from 1 05 to 1 85 mM per liter the average being 1 51 mM In five of these patients the calcium ranged from 5 8 to 7 4 mgm per 100 c c spinal fluid or from 1 45 to 1 85 mM per liter and in one of these patients whose spinal fluid calcium was 7 4 mgm a repeat spinal fluid in three months gave the same result

The total serum calcium ranged from 8 4 to 11 8 mgm per 100 c c or from 2 6 to 3 14 mM per liter of water the average being 2 81 mM The serum ionized Ca values were from 90 to 1 52 mM per liter of water the average being 1 5 mM The total calcium of the spinal fluid

to the influence of food in decreasing the absorption of alcohol from the stomach into the blood stream This problem was studied in patients with diabetes insipidus who took a normal-sized breakfast and one hour later the standard dose of alcohol The results were very striking The alcoholic symptoms and the concentration of alcohol in the blood and urine after the ingestion of food and alcohol were much lower than they were when food was omitted

Cerebrospinal Fluid

The spinal fluid in patients with diabetes insipidus of idiopathic origin was normal except for an increase of the calcium concentration in some cases The color cell content, pressure spinal fluid dynamics total

TABLE XVIII

COMPARISON OF FINDINGS IN CEREBROSPINAL FLUID (CSF) AND IN SERUM OF PATIENTS WITH DIABETES INSIPIDUS

Case		*Total Calcium Mgm*	*Phosphorus Mgm*	*Chloride Mgm*	*Total Protein Mgm*
1	CSF	7 2	1.6	448	90 0
	Serum	10.4	5.0	318	
	CSF	5 8	1.6	44	150 0
	Serum	11 6	4.4	335	
3	CSF	4	1.0	467	30 0
	Serum	8.4	3	41	
4	CSF	6 8	1 8	—	18 0
	Serum	10.0	3 6	—	
5	CSF	5 6	1 6	424	15 0
	Serum	10 2	3 9	375	
6	CSF	7.4	1.6	451	41 0
	Serum	11 8	4.0	35	

protein globulin gold sol sugar and chlorides were all within the normal range On the other hand cases of diabetes insipidus due to organic diseases such as brain tumor or infection may show the abnormalities in the spinal fluid caused by these coincidental lesions

Calcium, Phosphorus and Chlorides in the Cerebrospinal Fluid in Diabetes Insipidus — I[309] studied the concentration of the calcium[310] and phosphorus[311] in the cerebrospinal fluid in eight idiopathic and two post encephalitic cases of diabetes insipidus and compared the findings with

The average concentration of the spinal fluid calcium was slightly greater than that of the Ca^{++} content of the serum (1 51 vs 1 25 mM per liter) in a group of patients with diabetes insipidus A series of control patients showed no such difference between their serum Ca^{++} concentrations and cerebrospinal fluid calcium (1 [illegible]7 vs 1 24 mM per liter) Analyses for inorganic phosphate chloride and protein showed no significant variations from the normal

Basal Metabolism

The basal metabolism observed in 45 patients with diabetes insipidus ranged from minus 38 to plus 20 per cent in all except one instance A reading of plus 77 per cent was found in a boy aged 17 years with a

TABLE XXV

BASAL METABOLISM IN 45 PATIENTS WITH DIABETES INSIPIDUS

Number of Cases	*Metabolism per cent*
1	+77
2	+13 to +20
4	0 to + 7
11	− 1 to − 4
11	− 8 to −15
12	−20 to −29
4	−30 to −38

daily intake and output of about 30 liters This volume in rare instances rose to 48 liters and with pituitrin therapy decreased occasionally to 17 liters The patient in order to be comfortable had to take four liters of water and void a similar amount of urine during the period of observation for the metabolism test When he was 15 years old he had had meningitis which responded to antipneumococcic serum a year later he developed diabetes insipidus Autopsy revealed a cyst of the pars intermedia

The results shown in Table XXV were on the minus side in all but a few instances Sixteen of the cases had readings of minus 20 to minus 38 per cent There were no signs or symptoms of myxedema or hyperthyroidism

was appreciably greater than the ionized Ca concentration in the serum in a number of these cases the average difference being + 26 mM per liter of water as compared with + 03 mM in the control tests The results are shown in Table XXIV

The ratio of the spinal fluid calcium to the serum calcium ranged from 47 to 69 per cent the normal being 45 to 50 per cent The phosphorus content of the spinal fluid and serum was within the normal limits and the values were much the same as in the control tests

TABLE XXIV

COMPARISON OF CONCENTRATION OF IONIZED Ca IN SERUM AND TOTAL CALCIUM IN SPINAL FLUID IN PATIENTS WITH DIABETES INSIPIDUS

Case	*Serum Calculated* Ca++	*Spinal Fluid Total* Ca	*Spinal Fluid Ca minus Serum* Ca++
1	1 30	1 80	0 50
2	1 31	1 50	0 19
3	1 36	1.45	0.09
4	0.90	1.05	0 15
5	1 07	1 0	0 63
6	1 13	1 38	0 25
7	1 13	1.40	0
8	1 19	1 33	0 14
9	1.43	1 31	0 13
10	1.44	1 85	0.41
10	1 52	1 85	0 33
Average	1 25	1 51	0 6

The calcium results are recorded in mM (millimol) per liter of water

An elevated total protein of from 64 to 150 mgm per 100 c c of spinal fluid appeared in three cases two of which were associated with postencephalitic Parkinson s syndrome The serum protein determinations were normal

The chloride concentration in the spinal fluid varied from 382 to 49 mgm per 100 c c in these cases the normal being approximately 440 mgm The chloride in the blood was within the normal range

In *summary* the spinal fluid in idiopathic diabetes insipidus is normal except for a possible increase in the calcium content In other cases of diabetes insipidus due to infections or brain tumor the spinal fluid may show certain abnormalities depending on the underlying pathology

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ventional records of the electrical activity of the brain were obtained from electrodes placed in various positions of the scalp This procedure registers mainly cortical activity although disturbances deep within the brain may affect the surface area These were made to determine whether any disturbance in the physiological activity of any part of the brain could be detected by this method and possibly to find some local dis turbance which heretofore had not been observed in such cases

The results in the cases with diabetes insipidus of idiopathic origin showed normal electroencephalograms with a normal frequency of brain waves although two boys aged 13 and 16 years had in the tracings some signs of subclinical epilepsy However this is known to occur in normal people The twin sister of one of these boys showed the same type of tracing while the parents of the other boy had no evidence of sub clinical epilepsy

Electrocardiograms

Electrocardiograms in patients with diabetes insipidus were normal except in those who had complicating heart disease or hypertension

The electroencephalograms in the patient who had a total thy roidectomy for diabetes insipidus due to encephalitis were interesting This patient was a 35 year old male who had had diabetes insipidus for about 16 years After total thyroidectomy the basal metabolism de creased to minus -3 per cent and the fluid intake to about three liters a day He did not take thyroid extract Electroencephalograms made at this time showed a slow frequency of the brain waves with a rate of 6 or 7 waves per second Subsequently he was given eight grains of thyroid extract a day for a period of two weeks and the basal metabolism increased to plus 8 per cent and the polyuria and polydipsia returned Electroencephalograms now showed an increase in the frequency of the brain waves to normal with a rate of 10 or 11 per second

X ray Studies

X ray studies were made on the skull and other bones the gastro intestinal tract heart lungs and the genitourinary tract in groups of patients with diabetes insipidus

X rays of the skull including pneumoencephalograms in the idio

One might expect excessive water consumption to produce considerable changes in the basal metabolism of patients When these tests were made, the patients had been without pituitrin, and as a result they had to continue drinking water, in some cases up to a short while before the tests Nevertheless the metabolism usually was on the low side of normal The use of thyroid extract had no effect on the system of these patients except for increasing the polyuria

The administration of pituitrin did not produce any consistent effect on the metabolism of patients with diabetes insipidus as shown in Table XXVI

Bryan and Metzger[319] studied this problem by measuring the insensible loss of water in two cases of diabetes insipidus in which the water exchange was subjected to large fluctuations by administration and withdrawal of pituitrin The insensible water loss is of the same order of magnitude whether or not pituitrin is injected and evidently bears in diabetes insipidus its usual close relation to total metabolism These findings fit in with our results on basal metabolism

TABLE XXVI

BASAL METABOLISM IN PATIENTS WITH DIABETES INSIPIDUS WITH AND WITHOUT PITUITRIN THERAPY

Case	*On Pituitrin Metabolism percent*	*No Pituitrin Metabolism percent*
1	+ 1	0
2	− 1	− 7
3	−14	−11
4	−20	−19
5	+ 7	+13
6	+ 6	+16

Electroencephalograms

There has been increasing interest in the clinical use of electroencephalograms in attempting to localize disease of the brain or to observe disturbances in the physiological activity of certain parts of the brain Electroencephalograms were made in 10 patients aged 13 to 70 years with diabetes insipidus of idiopathic origin and in one patient who had a total thyroidectomy for diabetes insipidus due to encephalitis Con-

ureters were fairly well outlined were widened and relaxed The bladder was very large and atonic The dilatation and relaxation of the urinary tract varied with the cases There was a marked difference in the findings when pituitrin was administered Urographic examination with intravenous diodrast showed good excretion and concentration of the opaque medium through both kidneys five minutes after the injection with maximum concentration within 15 minutes The kidneys were slightly smaller than those seen without pituitrin therapy The pelves were of the intermediary type of normal size and regular in contour and definitely smaller than when no pituitrin was given The calices on both sides were normal and now showed normal cupping The ureters were well outlined with no deviation from the normal throughout their entire course The bladder filled but gave the appearance of thickened walls and trabeculations

It is important in studying intravenous urograms in diabetes insipidus to control the polyuria with pituitrin before performing the tests in order to obtain proper urograms

Diabetes Insipidus Associated with Other Conditions

There are certain important conditions such as pregnancy diabetes mellitus and other endocrine dysfunctions which may have an important relation to diabetes insipidus Worthy of comment in this connection also are other disorders such as gastrointestinal and cardiorenalvascular diseases allergies infections and blood dyscrasia

Diabetes Insipidus and Pregnancy

Diabetes insipidus is comparatively rare and the combination of this disease and pregnancy is even more uncommon It is seldom encountered in practical obstetrics and there have been only three such cases in approximately 50 000 deliveries at the Boston Lying in Hospital Yet I believe there are an appreciable number of mild and unrecognized cases of transient diabetes insipidus in apparently normal women during pregnancy In these instances the thirst and the unusual frequency to urinate have been considered part of the pregnancy Physiologically I feel this disturbance is related to diabetes insipidus

From the scarcity of reported cases of the combination of pregnancy

pathic cases were normal The bones showed delayed epiphyseal union in rare instances The skull in cases of diabetes insipidus due to brain tumor and xanthomatosis are discussed elsewhere in this chapter

Gastrointestinal x-ray studies in five patients with marked gastric symptoms revealed no abnormality in three cases and a duodenal ulcer in two with ulcer symptoms

X-rays of the heart and lungs were normal in uncomplicated cases of diabetes insipidus The size and shape of the heart remained the same whether or not posterior pituitary extract was administered

Renal calculi were found by retrograde pyelograms in a 51-year old male patient with suggestive symptoms of urinary calculi The genito urinary tract showed some interesting findings as revealed by intravenous urograms

Intravenous Urograms —In rare reports of cases of diabetes insipidus intravenous urograms have shown a poor concentration of the opaque medium in the kidneys after the injection of diodrast No definite con clusions concerning the kidneys in those cases could be drawn because the kidneys were defined poorly However, in these cases the patients apparently had no pituitrin therapy

We[3] have made intravenous urograms in six patients with diabetes insipidus with and without pituitrin therapy according to the standard method No fluids were taken for 13 or 14 hours before the intra venous injections when the patients were treated with pituitrin How ever when no pituitrin was administered the patients were unable to go without fluids for such a lengthy period A laxative was given the night before the tests were performed

The urograms were made on one day when the patients' diabetes insipidus was controlled with pituitrin and on another day when no pituitrin was administered and the symptoms of diabetes insipidus were present A dose of 20 c c diodrast compound solution (Winthrop Chemical Company) was injected intravenously This solution is of particular value in the urologic investigation of patients who can not refrain from fluids for the standard period of time Preliminary tests revealed that none of the patients had allergic hypersensitiveness to the diodrast X rays were taken 5 15 25 and 35 minutes after the injection

When pituitrin was not administered and the patients had marked thirst and polyuria urographic studies with intravenous diodrast showed an extremely rapid excretion of the opaque medium but poor concen tration throughout the examination The concentration was insufficient to outline the calices which were slightly blunted and dilated The

The first case was a 28 year old woman with diabetes insipidus for over 9 years Her history physical examination and laboratory tests including x rays were all essentially normal The polyuria was relieved with pituitrin In 1938 because of the various reports which suggested that the administration of estrogenic substance might suppress the diuretic principle of the anterior pituitary gland[3] the patient was injected with o ooo units of amniotin daily for 10 days without any effect on the fluid intake and output

The patient had her last menstrual period on June 4 1940 Her expected delivery date was March 31 1941 Physical examination was negative The pregnancy progressed normally for both patient and fetus She had no nausea or vomiting at any time and felt just as well as before pregnancy At the beginning the daily fluid intake and output were 10 to 12 liters the level before conception and then increased to a level of about 13 to 15 liters at the end of the 7th month of pregnancy About 2 weeks later the polyuria and polydipsia began to decrease appreciably so that shortly before the patient's delivery the daily fluid intake and output were about 3 liters as shown in Fig. 0

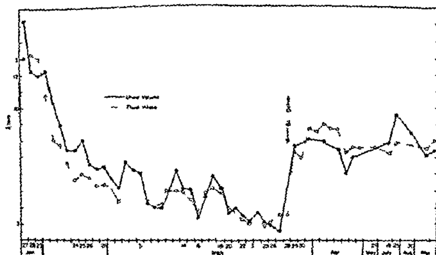


Fig 0 This chart records the daily fluid intake and urinary output during the last two months of pregnancy and after delivery of the patient in Case 1 during this period no pituitary extract was administered

She felt movements of the fetus in the fifth month The blood pressure remained constant at approximately 1 o/-o X ray films of the pelvis taken December 31 at the end of the sixth month of pregnancy showed a fetus consistent with the date

and diabetes insipidus the impression is obtained that few patients with this disease have children. However, in a thorough study of the literature it was found that these patients have children more frequently than one would expect[199]. At times they are quite prolific, some bearing as many as 11 offspring during the course of the disease. One of the best examples of fecundity of patients with diabetes insipidus was reported by Bellot and Brougniart[5]. An 40 year old Frenchwoman with an inordinate thirst from her earliest infancy had had 11 children in 10 pregnancies. Gee[91] described a patient with nine children. In the studies *of Weil[189] and his son[190] some of the women with hereditary diabetes* insipidus had 8 or 9 children. The pregnancies and birth were normal except that pregnancy usually increased the symptoms of the disease.

The various clinical effects of the combination of diabetes insipidus and pregnancy have been reported[331] and may be classified as follows: no effect of pregnancy on the disease; amelioration of the disease during pregnancy; aggravation of the disease during pregnancy; transitory diabetes insipidus during pregnancy, onset of the disease during pregnancy with persistence after delivery and transient and persistent appearance of the disease after delivery.

No Effect of Pregnancy on Diabetes Insipidus.—Several studies have shown that pregnancy had no effect on the polyuria and the polydipsia of diabetes insipidus[3, 9, 33]. Some of these patients had urine volumes as high as 16 to 20 liters a day. The patients of Boissard[33] and Artaud[34] excreted similar amounts of urine without any alteration during pregnancy.

Amelioration of Diabetes Insipidus During Pregnancy.—Several reports have shown that pregnancy during the course of diabetes insipidus resulted in an amelioration of the disease, and after delivery the polyuria and the polydipsia reappeared abruptly[3, 39, 331, 335]. The most illuminating report on this aspect of the problem is given by Duvoir, Pollet and Cachin[334], who treated a woman with diabetes insipidus during the course of three pregnancies and observed that the polyuria decreased in the sixth month of each and that the amount of urine became almost *normal during the weeks preceding each delivery.* However, on the day following delivery the daily urine increased suddenly to 12 liters, the level before pregnancy. Carter[333] noted that a patient had less thirst in the seventh month of pregnancy and that after a premature delivery the diabetes insipidus was considerably relieved and remained so during the years of subsequent observation. I have observed two cases of diabetes insipidus improved by pregnancy.

reports of diabetes insipidus and pregnancy deal with the transient occurrence of the disease which may appear during any stage of normal pregnancy [10 310 to 324] However in most cases the diabetes insipidus was apparent in the latter half of pregnancy usually in the fifth or sixth month Ordinarily the polyuria and the polydipsia ceased abruptly or 3 days after delivery although in some instances it persisted for as long as 17 days postpartum A case of transient diabetes insipidus occurred in one of my patients

This patient was a 36 year old woman who had no polyuria during or after pregnancy in 1936 In the present pregnancy the last menstrual period began on August 17 1941 The expected date of confinement was May 4 194 General physical examination and routine blood and urine tests were negative The patient s height was 64 inches and her weight was 140 pounds The pregnancy progressed normally until about the 5th month when she began to notice polydipsia and polyuria which increased progressively as the pregnancy advanced There was no unusual weight gain During the last 2 months of pregnancy the average daily urine volume was about 8 000 c c with a specific gravity of 1 00

On April 27 1942 x ray examination revealed a twin pregnancy Because of the excessive size of the abdomen and the extreme discomfort of the patient she was delivered prematurely on May 6 by a low cervical caesarean section under spinal anesthesia Normal twin boys weighing 5¾ pounds and 7⅛ pounds were delivered There was a double ovum twin fused placenta The polydipsia and polyuria disappeared abruptly after the delivery

The convalescence was uneventful The urine volume had been normal during the subsequent 6 years of observation and the specific gravity of the urine increased to about 1 015 The twins are 8 years old and normal

Transient diabetes insipidus has occurred also in successive pregnancies in approximately the same months of gestation In most of these cases the fluid intake and output increased to about 10 or 1 liters Edelman and Kritzman s[318] patient had a daily urine volume which reached a level of 25 liters Novak s[319] case was of interest because diabetes insipidus reappeared during 10 pregnancies and disappeared after each delivery Gansslen and Fritz [10] presented an unusual case of a healthy woman whose husband had diabetes insipidus During the terminal part of her first pregnancy she showed symptoms of diabetes insipidus which disappeared after delivery The baby of this pregnancy developed diabetes insipidus During her second pregnancy which resulted in a healthy baby the patient had no polyuria The authors

She went through a normal labor and was delivered of a normal baby on March 8, 1941. The day after delivery the fluid intake and output increased abruptly to a level of 8 liters and have remained at approximately a level of 10 liters during the subseqent years of observation. The patient had no edema at any time during or after pregnancy. The convalescence was normal.

During pregnancy the administration of pituitary extract cause a sensation of constriction of the uterus. On the other hand, pitressin, which is pituitary extract without the oxytocic principle, had an antidiuretic effect without the constrictive action on the uterus. This difference was revealed experimentally by the use of a tocograph which showed no uterine contractions after pitressin injection in contrast to the rhythmic uterine contractions after the injection of pituitary extract.

The placenta weighed 840 gm and was essentially negative. At birth the baby's weight was 8¼ pounds and height 55 cm. He is now 9 years old and has grown and developed normally.

Various laboratory data including blood volumes were obtained during various phases of pregnancy. The results shown were approximately the same as those found during pregnancy in the normal woman[336].

The second case, a 48 year old woman, had had diabetes insipidus since the age of 11 years. She had a daily fluid intake and output ranging from 10 to 17 liters. At the age of 3 she became pregnant, and during the last 2 months of pregnancy she thought that she was cured because her fluid intake and output were normal without the use of posterior pituitary solution. However, immediately after the delivery of a baby boy, when the placenta apparently was expressed, the severe thirst and polyuria recurred. Five years later she became pregnant again and during this period there was no change in her diabetes insipidus. This time she was delivered of a baby girl. In this case the diabetes insipidus has persisted and her menses are still regular and normal. The son aged 24 and the daughter aged 19 years are perfectly normal.

Aggravation of Diabetes Insipidus During Pregnancy.—A number of reports indicated that the polyuria and polydipsia of diabetes insipidus may be increased by varying degrees and during different periods of pregnancy[21, 3 9, 33, 338, 339]. Among 26 members with diabetes insipidus in a family of 73, Ellerman[illegible] found increased diuresis during pregnancy of the women with diabetes insipidus. In one patient, who gave birth eight times, the diuresis rose during each pregnancy from about 10 to approximately 20 liters daily. During the seventh pregnancy the daily quantity of urine reached 30 liters. I have not seen such a case.

Transient Diabetes Insipidus During Pregnancy.—The majority of

polyuria and the necrosis in the anterior and posterior lobes of the pituitary body revealed at autopsy

Their first case was a year old para who passed into profound shock following an acute inversion of the uterus after delivery of a living child From the sixth day of the puerpereum until her death on the tenth day she showed clinical evidence of diabetes *insipidus* with a daily urine output of about 7 liters An autopsy revealed that the anterior lobe of the pituitary showed massive necrosis and only occasional groups of healthy *cells remained about the periphery of the gland The posterior lobe* showed partial degenerative changes with loss of the normal compact structure of the neuroglia and a notable deficiency of pituicytes in the degenerated area

Their second case was a para 4 aged 34 years who had no prenatal care Shortly before admission she had an eclamptic fit and was in shock on arrival at the hospital The blood pressure was 130/80 and the urine contained considerable albumin The patient was delivered and had an accidental hemorrhage *The following 3 days her daily urine volume was about* 6 liters She died of acute pulmonary edema 84 hours after delivery The pituitary gland showed an almost complete necrosis of the anterior lobe with *few small islets of surviving cells The posterior lobe showed an area in* which degeneration of the neuroglia and deficiency of pituicytes were observed Since some normal anterior lobe tissue is necessary in the production of diabetes insipidus it is noteworthy that in these 2 cases a small proportion *of the anterior lobe cells survived*

Postpartum ischemic necrosis of the anterior pituitary is a relatively frequent complication in cases where delivery is attended by a severe degree of collapse Sheehan and Murdoch[3,4] who have contributed much towards our knowledge of this problem observed that the collapse in most cases is due to hemorrhage causing the pituitary necrosis Patients in whom the lesion *occurrs* may die soon after the appearance of the clinical signs of the necrosis or may live for years If they survive the clinical picture of a chronic state of anterior pituitary insufficiency may develop In fact the more severe cases show the characteristics of *Simmonds* disease

The cause of these variable effects of pregnancy on diabetes insipidus is questionable The pathology of diabetes insipidus during pregnancy has not been proved The excretion of water is controlled by *a balance of the hormones that diminish and produce diuresis* The variable effects apparently depend on which of these hormonal forces predominates It is suggested that the diuretic or antidiuretic hormone of the fetus may be transferred to some mothers and produce the effects

suggested the possibility that the hormone of the sick child was transferred to the mother during the terminal part of pregnancy and gave her the symptoms of the disease

Onset of Diabetes Insipidus During Pregnancy —Trench[3] observed a woman who developed diabetes insipidus with a daily urine volume of 10 liters during the fourth month of her fifth pregnancy The polyuria and polydipsia persisted after delivery Vickers[360] treated a patient who in the third month of her pregnancy developed diabetes insipidus with an output of approximately eight liters She had urinary retention and as a result had to be catherized, 3,250 c c of urine were obtained This woman miscarried a normal three month old fetus and the diabetes persisted after the miscarriage

Transient and Persistent Diabetes Insipidus After Delivery —Transient and persistent diabetes insipidus may also appear shortly after delivery Laurentie and Bashiou[361] presented a case of a 37 year old woman with a normal pregnancy On the day after delivery the patient suddenly began to void frequently and to drink with a rage Twenty one days later she developed violent frontal headaches photophobia and convulsions In addition a transient hypertension appeared The whole picture was typical of eclampsia however, there was no albumin in the urine The fluid intake was as high as 15 liters a day At one time the patient had to be catherized because of a dilated bladder and three liters of urine were obtained Within six weeks after the onset of convulsions all symptoms disappeared, and the patient was discharged from the hospital completely recovered Jansen[36] had a case of a woman with six deliveries but the diabetes insipidus appeared only during the last three pregnancies and persisted each time until 14 days postpartum In addition there are a number of miscellaneous studies on pregnancy[36 to 37] In my series there was one case of diabetes insipidus which began after delivery and persisted

This patient was a 51 year old woman with 5 children the youngest being 7 years old After the birth of her last child diabetes insipidus commenced She took pituitrin for 4 years with relief and then the diabetes insipidus became milder requiring very little or no pituitrin An attack of influenza aggravated the polyuria and polydipsia which were again controlled with pituitrin

A study of the pathology of diabetes insipidus appearing after delivery has been published recently by Spain and Geoghegan[373] The striking clinical features of their two cases were the extreme degree of

the uterus If pituitary extract is given small doses such as 1 to 3 minims may be injected The intranasal use is advantageous because it eliminates the marked effect on the uterus noticed with injection However intranasal application does not appear so effective during pregnancy as in the normal nonpregnant state Pitressin appears safer and more valuable than pituitary extract because it lacks the oxytocic principle

Diabetes Insipidus Associated with Diabetes Mellitus

The association of diabetes mellitus and diabetes insipidus is rare In our series one true case of diabetes mellitus occurred with diabetes insipidus although in a few brain tumor cases there were changes in the sugar tolerance suggesting diabetes mellitus Cases have been observed in which the two diseases coexisted[3] [3] or in which there was a transition from diabetes mellitus to diabetes insipidus[381] [3] and vice versa[388 to 3] In some instances there is a question in my mind as to whether true diabetes mellitus was present

In 1897 Senator[3] first recognized the relationship between diabetes mellitus and diabetes insipidus He described a 43 year old woman with diabetes insipidus since childhood and glycosuria since the age of 40 years She failed progressively and died a year later Greene and Gibson[381] who found in the literature the combination of these two diseases in only 20 cases also reported the case of a woman who had diabetes mellitus at the age of 5 years Later she became pregnant and developed coma which was controlled with insulin Shortly after this diabetes insipidus appeared and the pregnancy terminated at full term with a normal labor She was controlled with diet the administration of 55 units of insulin daily and with the nasal insufflation of posterior pituitary extract

McPherson[384] had a patient who died and autopsy revealed a relative hyperplasia of the eosinophilic cells of the pituitary The case of a Talbott and associates[385] showed x ray findings suggestive of a small tumor in the region of the pituitary body Joslin's[38] patient had for six years a daily fluid intake and output of about five gallons which gradually decreased to normal and then true diabetes mellitus appeared

The concurrence of these two diseases has been observed generally in acquired diabetes insipidus and rarely in the inherited type In an extensive study Forssman [1] found two cases of hereditary diabetes in

of each in the mother The marked improvement of the diabetes insipidus toward the end of pregnancy in our cases conceivably was due to the antidiuretic action of the posterior pituitary gland of the fetus or to the increased activity of that of the mother On the other hand, the patient of Gansslen and Fritz[10] suggests the possibility that the diuretic hormone of the fetus was transferred to the mother with the resultant temporary symptoms of diabetes insipidus

Furthermore, follicular hormone which normally is increased during pregnancy has been used in large doses with success in the treatment of diabetes insipidus without pregnancy by Troisier[3] and Beltrametti[376], although I[377] was not able to obtain this effect Muller[33] referred to a non-pregnant woman with sparse menses and polyuria that diminished when the menses became regular

The diuretic hormones most probably are of anterior pituitary or placental origin Henriet[380] referred to a polyuric patient with a hydatidiform mole, a condition in which the urinary prolan is markedly increased In addition he commented on a pregnant woman who in spite of edema had a significant polyuria The determination of her daily prolan excretion gave the enormous figure of 38 000 rabbit units The diuretic action of the thyroid hormone should be considered

Forssman[1] found in hereditary diabetes insipidus that diabetes insipidus appeared not infrequently for the first time during the second third or fourth pregnancy and reappeared with subsequent pregnancies with few exceptions In one case a woman after four bouts of transient diabetes insipidus gravidarum each one more intense than the last, gradually acquired permanent diabetes insipidus

The duration of labor as well as the birth of children in patients with diabetes insipidus is normal and spontaneous Harding[378] reported four women with diabetes insipidus and pregnancy, aged 19 to 28 years who were delivered normally although two had cesarean sections There are also rare cases reported with premature delivery In contrast, in experimental diabetes insipidus cats had either prolonged labor or were unable to deliver their young[379] Fisher Magoun and Ranson[379] believed this disturbance to be due to a deficiency in the pituitary oxytocic hormone consequent to the experimental diabetes insipidus

Lactation as it appeared in our cases and as it is reported in the literature is similar to that in the normal woman In some cases there is an adequate milk supply and in others practically none

In the treatment of a pregnant patient with diabetes insipidus care must be taken about the use of pituitary extract because of its effect on

Moloney[201] as well as one of Rutledge and Rynearson[1 2] was relieved by posterior pituitary extract The diabetes mellitus should be controlled with proper diet and with insulin when necessary Although Blotner and Fitz [3] have shown that the injection of pituitary extract has an antagonism toward insulin in its effect on the blood sugar in rabbits it does not interfere with the practical treatment of diabetes mellitus with insulin

In some instances the glycosuria may be controlled with a diet alone as in Schuntermann's[1 0] case while the polyuria was relieved by pituitary extract Before the days of insulin other cases such as those of Heiberg[401] and Freund[1 2] died of diabetic coma The use of insulin in controlling the glycosuria already has been described in certain cases[201] [3] [391] On the other hand there may be resistance to insulin as reported by Cipriani and associates[403] in an unusual case with diabetes mellitus diabetes insipidus acromegaly pituitary adenoma and goitre and in a case of di Gughelmo[404] in which there was diabetes mellitus polyuria and a lesion of the pituitary gland

Gray and Moffat[1] observed the presence of diabetes mellitus and diabetes insipidus in a 53 year old Mexican male who was controlled with insulin and pituitrin This patient died of ruptured appendix At autopsy it was found that the islet cells were nearly replaced by a pale hyaline material The pathological changes in the pituitary gland were limited to the pars neuralis and pars intermedia where the delicate neurofibrils of the former had been replaced by dense collagenous tissue which surrounded the few visible colloid cysts of the pars intermedia Only a few of the deeply staining cells of the pars intermedia were seen in this dense connective tissue which extended into the pars neuralis but did not reach the stalk Numerous foci of lymphocytes were scattered throughout the collagenous tissue Vascular changes were minimum In our series there was one true case of diabetes mellitus existing with diabetes insipidus

This patient was a 16 year old girl who had had diabetes mellitus since the age of years and diabetes insipidus since the age of 7 or 8 years She had a fluid intake of about 6 liters daily and a blood sugar level which was at times above or below 400 mgm The blood cholesterol was 3,8 mgm per cent Insulin and pituitrin controlled the patient s diabetes mellitus and diabetes insipidus In addition to these diseases she also had deafness and optic nerve atrophy She had a right frontal bone flap operation for exploration of the optic chiasma No tumor was found However there was con

sipidus complicated with diabetes mellitus In both cases the patients became ill at the age of 50 years and were regulated without insulin He too encountered a number of cases of diabetes mellitus among the relatives of the diabetes insipidus patients, a fact to be expected in a large group of people A possible genetic connection between these two diseases has been sought in the occurrence of diabetes insipidus and diabetes mellitus in the same family Steiner[390] noted several cases of diabetes mellitus in family investigations based on probands with diabetes insipidus However he did not determine whether the number of cases of diabetes mellitus is greater than a corresponding large material selected at random can be expected to contain

The significance of the coincidence of these two diseases is rather uncertain Possibly they have a related pathogenesis which become more apparent in light of the advancing knowledge of the physiology and pathology of the pituitary gland in these diseases Houssay[391], Long[39] and Young[393] have shown a relation between the pituitary gland and diabetes mellitus These investigators and others, injecting extracts of the anterior lobe of the pituitary gland into certain animals, produced hyperglycemia, glycosuria and polyuria As the result, there was destruction of the islands of Langerhans with a diminished insulin content of the pancreas due to excessive stimulation by these extracts[394] The experiments gave rise to the hypothesis that diabetes mellitus is related to an increased secretion of the diabetogenic hormone from the anterior lobe of the pituitary gland

Diabetes insipidus has been produced[33] by injuring the supraoptic hypophyseal tract which resulted in diminished production of the antidiuretic substance from the posterior lobe of the pituitary gland Furthermore there is evidence to suggest that diabetes insipidus is dependent on a functioning of the anterior lobe[39] as well as a deficient function of the posterior lobe Possibly in these cases of diabetes insipidus associated with diabetes mellitus there is an unusually excessive secretion of the anterior lobe of the pituitary gland over a considerable period of time which may produce diabetes mellitus as well as diabetes insipidus Other interesting pathological cases in which these two diseases were associated are one with hypophyseal infantalism[396] and another[397], who had diabetes insipidus and central nervous system syphilis and who years later developed diabetes mellitus

Treatment—The treatment consists in managing these diseases as though they existed independently Adequate pituitary therapy should be given to relieve the diabetes insipidus A 63-year old patient of

Moloney[398] as well as one of Rutledge and Rynearson[399] was relieved by *posterior pituitary* extract The diabetes mellitus *should be controlled* with proper diet and with insulin when necessary Although Blotner and Fitz[3] have shown that the injection of pituitary extract has an antagonism toward insulin in its effect on the blood sugar in rabbits it *does not interfere with the practical treatment of diabetes mellitus with insulin*

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siderable evidence of an old arachnoiditis in the basal region particularly in the cysterna chiasmatica By x-ray she was found also to have hydroureters and hydronephrosis

Digestive System and Diabetes Insipidus

Except for polyuria and polydipsia the most common disturbance associated with untreated diabetes insipidus in my series is related to the gastrointestinal tract However the frequent gastrointestinal symptoms largely functional and caries of the teeth have been discussed under "Symptoms of Diabetes Insipidus" There have occurred rarely organic diseases such as duodenal ulcer appendicitis cholecystitis and a case of carcinoma of the rectum Colitis marked constipation non infectious diarrhea gastrointestinal hemorrhage or liver disease were absent in my cases

Allergy in Diabetes Insipidus

Allergic conditions such as hay fever and mild asthma appear more frequently in patients with diabetes insipidus than in non diabetics The most common allergies are due to the intranasal and subcutaneous administration of pituitary extract The intranasal use of the drug often produces rhinitis and aggravation of mild asthma necessitating the omission of this method However such patients tolerate the drug administered subcutaneously Pituitary injection often produces a local burning reaction which may become indurated and persist for as long as 24 hours These reactions have not been severe enough to require withdrawal of the drug Furthermore pitressin tannate in oil has not produced such reactions I have not seen generalized allergy urticaria or lipodystrophy following pituitary injection as found in diabetes mellitus after the use of insulin The reported resistance to pituitrin[406] may be an allergic phenomenon and has not been encountered in my cases

Cardiorenal Vascular Disease in Diabetes Insipidus

Arteriosclerotic changes were absent clinically in the younger patients with diabetes insipidus of 20 or 30 years duration and infrequent in the older persons with this disorder There were no complaints of circulatory disturbances in the extremities Roentgenograms of the

legs in a number of cases failed to show evidence of sclerosis of the peripheral arteries The radial temporal and dorsalis pedis arteries appeared normal Furthermore vascular disease was relatively unapparent in postmortem examinations of 15 cases of diabetes insipidus due to various causes including two of idiopathic origin Since patients with diabetes insipidus tend to have an elevated blood cholesterol [1] the rare incidence of arteriosclerosis is interesting in view of Leary s work[1] which suggests atherosclerosis as a disorder of cholesterol metabolism

Definite hypertension occurred in six of our cases all females In two women aged 40 and 48 years the blood pressure was 165/110 In three others aged 51 to 54 years the blood pressure was 170/110 ,60/140 and 70/150 the last being in a markedly obese cardiac patient with diabetes insipidus for 46 years A sixth woman aged 69 years with a blood pressure of 21 /105 had diabetes insipidus for four weeks and x rays showed calcification of the internal carotid artery The arteriosclerosis in this case possibly produced diabetes insipidus In the old days cerebral arteriosclerosis or cerebral hemorrhage was a fairly common factor in the etiology of diabetes insipidus

In our series three patients with diabetes insipidus had heart disease One was the 51 year old markedly obese woman with diabetes insipidus for 46 years She had a blood pressure of 270/150 and chronic myocarditis with edema of the legs for about 3 years When she was given digitalis and general treatment the heart and the edema improved A second patient was a 73 year old obese man who had some dyspnoea and edema of the legs even without pituitary therapy during the last few years of his life He had had diabetes insipidus for over 5 years Autopsy revealed hypertrophy of the heart muscle According to the literature one seldom hears of edema in diabetes insipidus even in patients with heart trouble Our two patients had edema even when they had marked polyuria Myocardial infarction occurred in a third patient a 67 year old man with diabetes insipidus for over 45 years He weighed 1 pounds and was 66 inches tall His progress has been satisfactory during the two years of observation after the coronary occlusion

Disease of the kidneys is rare in diabetes insipidus except for the physiological disturbance in the reabsorption of water by the tubule I have not seen any case of acute or chronic nephritis in diabetes insipidus

It has been suggested that patients with polyuria and polydipsia run less chance of developing urinary calculi and their accompanying complications However I have observed urinary calculi in a 51 year old

patient with diabetes insipidus with improvement after removal of the calculi A second patient 27-years old had transitory symptoms of urinary calculi not verified by x-ray

Infection in Diabetes Insipidus

During 20 years of study I have found such infections as pulmonary upper respiratory and genitourinary infections to be rare I have not seen a case of lobar pneumonia in diabetes insipidus Even infections of the skin are uncommon Some patients as well as members of their family have noticed and commented upon this fact The polyuria and polydipsia are not made more severe by the infections If anything they appear somewhat lessened particularly in patients with colds In the latter individuals the ingestion of salicylates may decrease the symptoms of diabetes insipidus

Tuberculosis had been considered a significant complication in diabetes insipidus before the use of pituitrin in the treatment of this disease In the old days many of the patients were debilitated and pulmonary or lymph node tuberculosis was a frequent concomitant of diabetes insipidus and often the cause of death The susceptibility of the patient with diabetes insipidus to tuberculosis apparently depends on modern hygiene and control of the polyuria and polydipsia The incidence of tuberculosis has decreased markedly in diabetes insipidus as a result of these advances In our series of 112 cases there were two with pulmonary tuberculosis One was a young man who had inherited diabetes insipidus from his father but did not follow the prescribed therapy for the disease His general care and hygiene were poor Tuberculosis developed and caused his death several years later at the age of 30 The second case was a 19-year old boy who had diabetes insipidus for nine months and died of tuberculous pneumonia

Endocrine System and Diabetes Insipidus

The pituitary body and its associated structures hold the center of the stage in any dissertation on the fundamental defect in diabetes insipidus However there are a number of endocrine disorders which influence or modify the effect of the pituitary gland Disturbances in the

endocrines such as the thyroid parathyroids gonads and adrenals have been discussed under various other sections

Blood Complications in Diabetes Insipidus

In cases of diabetes insipidus of idiopathic origin there has been no blood complication On the other hand leukemia Hodgkin s disease and aplastic anemia have resulted in diabetes insipidus Secondary anemia has appeared in some cases of diabetes insipidus due to certain pathological conditions The general blood findings in diabetes insipidus are presented under Laboratory Studies

Diagnosis

The diagnosis of diabetes insipidus is a comparatively simple matter as a rule The diagnosis is based on the cardinal symptoms namely polydipsia polyuria and severe thirst which persist during the 24 hours of the day when untreated If a patient is able to sleep through the night without having to drink and void it is quite certain that he does not have diabetes insipidus The daily fluid intake and output in most of the untreated cases are approximately 10 liters a day and the urine is colorless with a persistently low specific gravity of about 1 000 or 1 003 when the fluid intake is not restricted If the specific gravity is in the neighborhood of 1 010 or above the diagnosis of diabetes insipidus appears unlikely unless the fluid intake was restricted In contrast, in the patient with diabetes insipidus treated with sufficient posterior pituitary injections the fluid intake and urine volume decrease rapidly to normal Then the urine assumes a normal amber color with a specific gravity which rises to about 1 020 or more

The urine in diabetes insipidus contains no abnormal elements unless there is some complicating condition It is well to exclude such diseases in the differential diagnosis as diabetes mellitus polycystic kidneys chronic nephritis and certain types of secondary infections However in these cases the diagnosis usually is made quite readily

At the Mayo Clinic[108] a procedure for the diagnosis of diabetes insipidus is as follows The patient is made to refrain from drinking any fluids for as long a period as possible without extreme discomfort Then a urine specimen is obtained If the specific gravity of this urine specimen is more than 1 010 the presence of diabetes insipidus is considered

most unlikely In four of their 34 cases of diabetes insipidus the specific gravity was 1 011

Occasionally there is difficulty in distinguishing this disease from hysteria Hysterical patients may show some characteristics of diabetes insipidus and the question arises as to whether the polyuria and the polydipsia are manifestations of the mental condition When a concentration test is performed in hysterical patients, the type of polyuria can be recognized as not due to diabetes insipidus by the prompt reduction of the urinary output and a simultaneous increase of the specific gravity of the urine to 1 020 or even 1 030 In diabetes insipidus under the same conditions the amount of urine will continue to be greater than normal and the specific gravity as a rule will continue to be low

Blumgart [4] has found the following procedure of great value in the differential diagnosis of diabetes insipidus possibly associated with hysteria The dose and frequency of pituitary extract injection which diminishes the water intake but does not control the symptoms completely are established Sufficient posterior lobe extract is given a patient with a daily fluid intake of 10 liters to reduce the volume to approximately five liters In the middle of each interval between the injections of posterior lobe extract, the equivalent amount of sterile physiological saline solution is injected At various times injections of saline are substituted for the pituitary injections at other times the reverse is done Thus the amount of extract administered can be varied greatly In true diabetes insipidus there is close correspondence between the water intake and the amount and frequency of the pituitary extract administered No such close correspondence is seen in hysteria Some hysterical patients show a great reduction in water intake after saline injections, others continue to drink large amounts of water even when the dosage of pituitary extract is increased They may retain considerable amounts of the ingested water within their bodies under such circumstances and show the signs of water intoxication with nausea vomiting headaches and giddiness This method at times may be of the utmost diagnostic importance particularly in the group of patients showing mental deterioration and defective judgment following encephalitis lethargica

Prognosis

A person may have diabetes insipidus and still be healthy Regardless of the age of the patient the prognosis of diabetes insipidus of

proven idiopathic origin is good. Prognosis of such cases associated with other conditions like brain tumors, Parkinson's disease and xanthomatosis depends largely on the underlying pathological condition.

Contrary to the belief of some individuals, patients have lived for 10 to 45 years or even longer without showing any scars due to this disease. Persons, who have inherited the disease, have an especially favorable prognosis as one can see from the longevity of the cases in the Weil[189, 190] pedigree. Three of their patients lived to the ripe ages of 83, 87 and 92 years. The study of Forssman[23] corroborates Weil's results. Apparently patients with this disease may look forward to a long life expectancy unless some intercurrent condition appears. However, a number of these intercurrent diseases, such as infections which appeared frequently in the old days, are unlikely now because of modern therapy and hygiene which prevent debility and treat complicating conditions.

The excessive consumption of water over a period of years does not have a detrimental effect on the cardiovascular system. Arteriosclerosis is relatively uncommon in diabetes insipidus.

A person with this disease should be expected to live a normal life. Psychologically people with diabetes insipidus can live happily and usefully. They should not feel inferior or hindered because of their disorder. Children with diabetes insipidus should be considered a normal part of the household, and their parents should plan their future in the same way they would for healthy boys and girls.

Patients with diabetes insipidus may marry and have a happy marital life. Normal pregnancy and normal delivery are to be expected. Furthermore, the disease may improve during pregnancy. Surgery, when necessary, can be performed and any type of anaesthesia employed without any greater risk than normal.

A person with diabetes insipidus is a normal individual, mentally and emotionally, whose major defect lies in the supraoptic-hypophyseal system, which regulates the secretion of the posterior lobe of the pituitary gland. Medical science may now control this dysfunction. These people, whether young or old, should take a normal place in society.

Treatment

The ideal treatment of diabetes insipidus, naturally is the eradication of the cause, if possible. Unfortunately, the successful treatment of the cause of this disease is quite rare. However, it is now possible to

control the polyuria and polydipsia by the administration of posterior pituitary extracts. Of importance for the patients' comfort posterior pituitary therapy relieves these symptoms regardless of the etiology of the diabetes insipidus.

Posterior Pituitary Therapy

In 1913 von den Velden[22] and Farini[23] independently found that extracts of the posterior lobe of the pituitary gland relieved the polyuria and the polydipsia of human patients with diabetes insipidus. This observation led to the treatment of diabetes insipidus with posterior pituitary solution. So far none of the active principles of the posterior lobe of the pituitary gland has been isolated in chemically pure form. Abel and associates[109] have isolated a tartrate of high purity possessing pressor, oxytocic and antidiuretic properties. Kamm and associates[110], as well as Stehle[111] and other investigators, have separated from pituitary extract two fractions, namely pitressin and pitocin. Various preparations of the posterior lobe of the pituitary gland are available for clinical use.

Forms of Extracts of Posterior Pituitary. — Nomenclature and Potency.—According to the U. S. Pharmacopeia, XIII, 1947[112], the three synonymous designations for the soluble extract of the posterior lobe of the pituitary gland are *posterior pituitary solution*, *pituitary solution* and *posterior pituitary injection.*

Posterior pituitary solution, or its equivalent, is a solution in water for the injection of the water soluble principles of the posterior lobe of the pituitary body of healthy domesticated animals used for food by man. The potency of posterior pituitary solution is such that 0.1 c.c. of the solution possesses an activity equivalent to 1 U.S.P. posterior unit. The potency of 0.5 mgm. of U.S.P. posterior pituitary (standard) represents 1 U.S.P. unit.

Posterior pituitary is the official title of the powdered extract of the posterior lobe of the pituitary gland. It is the clean, dry and powdered posterior lobe obtained from the pituitary body of domesticated animals used for food by man. The potency of posterior pituitary is such that 1 milligram possesses an activity equivalent to not less than 1 U.S.P. posterior pituitary unit.

Pitressin tannate in oil, a compound solution of posterior pituitary with slow absorption and a greatly prolonged antidiuretic effect, is a

water-soluble chemical combination of the pressor fraction of the posterior lobe of the pituitary gland with tannic acid. The pressor fraction is precipitated with tannic acid and the precipitate is removed by filtration, washed and dried under aseptic conditions. Five pressor units of pitressin tannate are suspended in 1 c.c. of peanut oil.

Commercial preparations.—The word, *Pituitrin*, identifies the manufactured extract of the posterior pituitary gland. This commercial preparation is obtained in two strengths; (1) obstetrical pituitrin containing 10 units per c.c. and (2) surgical pituitrin containing 20 units per c.c. Surgical pituitrin is twice as strong as obstetrical pituitrin and has twice the oxytocic potency of pitocin.

Pitressin, which contains 20 pressor units in each c.c., is of the same strength as surgical pituitrin and designates the pressor, blood pressure raising and antidiuretic principles of the posterior lobe of the pituitary gland in a solution substantially free from the oxytocic principle. One pressor unit is the pressor activity exhibited by 0.5 milligram standard U.S.P. posterior pituitary powder. Pitressin instead of pituitrin should be used in diabetes insipidus with pregnancy to avoid the oxytocic effect.

One gram of posterior pituitary powder U.S.P. is the equivalent of six grams of fresh posterior lobe pituitary substance. It contains all the principles of pituitrin.

Since the expense of these items is an important factor to many patients, the comparative cost of the various preparations is listed below.

Preparation	*Amount*	*Cost*
Posterior pituitary powder	4 grams	$ 5.00
Posterior pituitary powder	100 capsules, 45 mgm.	$ 7.00
Pituitrin, obstetrical strength	100 1 c.c. ampoules (20 units)	$22 50
Pituitrin, surgical strength	100 1 c.c. ampoules (20 units)	$37.50
Pitressin	100 1 c.c. ampoules (20 units)	$49 50
Pitressin tannate in oil	100 1 c.c. ampoules (5 units)	$37.80

Administration of Posterior Pituitary Extract.—The preparations of posterior pituitary may be administered by several methods. The solution may be given subcutaneously, intramuscularly and intranasally. The powder may be taken intranasally. Pitressin tannate in oil may be administered subcutaneously or intramuscularly. The dose of posterior pituitary solution is .5 to 1.0 c.c. when injected and is required two to four times a day. There is an immediate drop in the fluid intake and output after the administration of this extract, and when the drug is

omitted, there is a rapid rise in the intake and output to the original level. Fig. 21 illustrates the effect of posterior pituitary solution in a patient

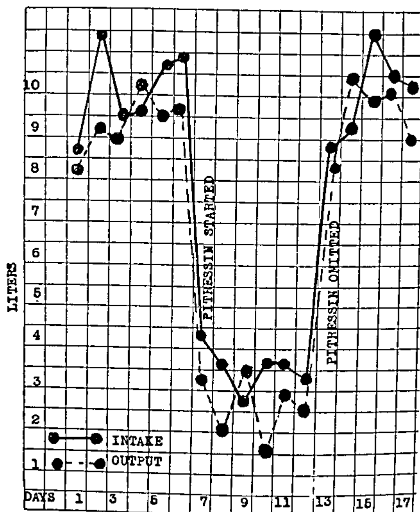


Fig. 21. Effect of the injection of 1 c.c. of pitressin 4 times a day on the daily fluid intake and output of a patient with diabetes insipidus.

with diabetes insipidus. The effect of each injection lasts for about five to eight hours depending on the individual patient. However, most patients do not take pituitary solution as soon as the effect wears off; consequently many are not under complete control at all times as when pitressin tannate in oil is taken.

Posterior pituitary solution should be used at the specific times which give the patient most comfort from the polyuria and polydipsia; at his bedtime to insure a good night's sleep, in the morning on arising and during the day whenever necessary. In the treatment of a patient in the *hospital ward it is important to specify the exact time of the therapy.* Otherwise, if an order is written for pituitary solution three times a day, it is likely that it would be administered at 10:00 A.M., 2:00 P.M., and 6:00 P.M., or it would fall into the hospital's routine three times a day orders when most drugs are given.

The effectiveness of the *intranasal application of posterior pituitary* was demonstrated first by Blumgart[274]. He showed that it checked the polyuria and polydipsia almost as effectively as the hypodermic injection, the frequent administration of which often causes the patient discomfort. This method is not accompanied by unpleasant gastrointestinal and circulatory reactions.

The pituitary extract may be sprayed into the nose so as to be deposited mostly in the roof of the nasopharynx, or the extract may be applied by the means of a cotton pledget, the last being a most effective method. A piece of absorbent cotton the size of the end of a finger is soaked with .5 or 1 c.c. of the posterior pituitary solution by filling a 1 c.c. syringe with the desired amount, inserting the needle into the *cotton and discharging the content of the syringe; it also may be soaked* by dipping the cotton into the posterior pituitary solution vial. The cotton then is saturated by light squeezing so that no pituitary extract will be lost. The pledget then is taken with a forceps and deposited in one nostril at the level of the middle turbinate, where it should be kept for about three or more hours to permit a continuous absorption. If the cotton pledget is too low in the nostril, little absorption takes place. Generally the nostrils should be alternated. The nose frequently becomes irritated and sensitive, and the patient has the sensation of a cold.

My experience has shown that this form of treatment is effective in all cases, but that it may produce less marked results than the pituitrin injection. Yet, when the pituitary solution is applied intranasally in more frequent *doses, it has approximately the same effect as the subcutaneous* injection. I have found that posterior pituitary solution, administered sublingually and between the gums and mucous membranes of the mouth, has afforded some relief but not enough for practical purposes. This solution also is absorbed to a slight degree when applied intravaginally.

It has been shown[113] that the intranasal insufflation of posterior pituitary powder in doses of from 40 to 50 milligrams three times a day is as effective in maintaining a normal water balance with alleviation of all symptoms as 1.5 to 2.0 c.c. of double strength solution of pituitary administered subcutaneously. The usual patient requires three to four such doses a day to maintain a water balance with alleviation of the polyuria and polydipsia. The effect of each dose varies from four to eight hours.

Insufflation outfits may be used for the introduction of posterior pituitary powder into the nose, but they must be clean and dry. The nozzle must be inserted about three-quarters of an inch inside the nose in order to be high enough. Then the breath is held, and the bulb of the insufflator is squeezed with sufficient force to propel the powder on to the upper absorptive surfaces of the nose. The process may then be repeated in the other nostril. Excessive force should not be used in blowing the powder into the throat. The nose should not be blown for some time after the administration of the powder. The posterior pituitary powder also may be inhaled by taking a pinch of it from the finger tips or by inhaling it from a snuff box.

Choay and Choay[114] have used poterior pituitary powder inhalation for twenty years to control the thirst and polyuria in more than 100 cases of diabetes insipidus. The powder was taken into the nose in the manner of snuff. Their best results were obtained with three to five doses of 0.01 gm. in the course of a day and with one dose of 0.02 gm. at night before the patient went to bed. In the average case they found that the effect lasted three to six hours during the day and for six to ten hours during the night.

Contraindications to the method are various types of rhinitis. Even a simple coryza or cold may cause failure of absorption of the pituitary powder. Anterior rhinoscopy at times may be of value as a preliminary to the administration of the extract.

Rees and Olmsted[115] in 1922 found that desiccated posterior lobe substance in salol coated capsules taken orally controlled polydipsia and polyuria. However, when given by mouth without capsule, the extract had no effect. I have used tablets of pituitary extract by mouth in a number of cases without effect on diabetes insipidus.

Reactions to Effects of Posterior Pituitary Extract. – The separation of pitressin and pitocin from pituitary extract necessitated apportioning these multiple pharmacodynamic actions[116]. Pitressin elicits the cardio-

vascular, the respiratory, renal, intestinal and certain metabolic effects whereas pitocin exerts the oxytocic action. Both substances cause hyperglycemia and act as antagonists to insulin[252]. Although solution of pituitary U.S.P. or pitressin are said to be contraindicated in hypertension, the therapeutic doses of either of these solutions given intramuscularly, subcutaneously or intranasally do not cause any significant rise in blood pressure in man in spite of the resultant pallor of the patients.

A brief fall in the pulse rate, oxygen consumption and cardiac output is followed by a more prolonged rise[117]. The decreased cardiac output after the injection of solution of the posterior pituitary or pitressin is due largely to a coronary constriction which may be obviated by administration of adrenalin or ephedrin[118].

Starr and associates[119], studying the action of pitressin in three cases of diabetes insipidus, found no change in the cardiac output, respiration, metabolic rate and electrocardiograms in two cases. On the other hand, Melville[118] found pituitrin produced T wave changes, which represented ventricular effects resultant from anoxemia secondary to coronary constriction.

Resistance to Solution of Posterior Pituitary.—The reported resistance to solution of posterior pituitary has not occurred in my patients, although at times some of them required more pituitrin than others for the control of the polydipsia and polyuria. Out of 74 cases of diabetes insipidus in the literature Fradiss[104] collected 12 cases which were refractory to pituitrin therapy. In three instances antisyphilitic treatment was successful after the failure of the pituitrin.

On the basis of two cases Biggart[96] suggested an anatomical lesion as a possible cause for resistance to the antidiuretic factor. His first patient, a 19-year old boy and an imbecile with paralysis agitans, had a daily fluid intake of about 15 liters. His second patient was a 43-year old man with recent diabetes insipidus, who responded to pituitrin for two months and then became refractory. Biggart believed that damage to the tuberal nuclei with or perhaps without concommitant damage to the supraoptic hypophyseal system resulted in a form of diabetes insipidus not controlled by the antidiuretic factor.

However, I do not believe that an anatomical basis per se is the cause of the resistance to pituitrin. In diabetes insipidus the decreased reabsorption of water in the tubule of the kidney is restored to normal following the administration of pituitrin. This condition would be expected to occur whether or not the tuberal nuclei are affected. It appears more likely that in these refractory cases that there is present

It has been shown[113] that the intranasal insufflation of posterior pituitary powder in doses of from 40 to 50 milligrams three times a day is as effective in maintaining a normal water balance with alleviation of all symptoms as 1.5 to 2.0 c.c. of double strength solution of pituitary administered subcutaneously. The usual patient requires three to four such doses a day to maintain a water balance with alleviation of the polyuria and polydipsia. The effect of each dose varies from four to eight hours.

Insufflation outfits may be used for the introduction of posterior pituitary powder into the nose, but they must be clean and dry. The nozzle must be inserted about three-quarters of an inch inside the nose in order to be high enough. Then the breath is held, and the bulb of the insufflator is squeezed with sufficient force to propel the powder on to the upper absorptive surfaces of the nose. The process may then be repeated in the other nostril. Excessive force should not be used in blowing the powder into the throat. The nose should not be blown for some time after the administration of the powder. The posterior pituitary powder also may be inhaled by taking a pinch of it from the finger tips or by inhaling it from a snuff box.

Choay and Choay[114] have used poterior pituitary powder inhalation for twenty years to control the thirst and polyuria in more than 100 cases of diabetes insipidus. The powder was taken into the nose in the manner of snuff. Their best results were obtained with three to five doses of 0.01 gm. in the course of a day and with one dose of 0.02 gm. at night before the patient went to bed. In the average case they found that the effect lasted three to six hours during the day and for six to ten hours during the night.

Contraindications to the method are various types of rhinitis. Even a simple coryza or cold may cause failure of absorption of the pituitary powder. Anterior rhinoscopy at times may be of value as a preliminary to the administration of the extract.

Rees and Olmsted[115] in 1922 found that desiccated posterior lobe substance in salol coated capsules taken orally controlled polydipsia and polyuria. However, when given by mouth without capsule, the extract had no effect. I have used tablets of pituitary extract by mouth in a number of cases without effect on diabetes insipidus.

Reactions to Effects of Posterior Pituitary Extract. — The separation of pitressin and pitocin from pituitary extract necessitated apportioning these multiple pharmacodynamic actions[116]. Pitressin elicits the cardio-

posterior pituitary and of pitressin appears to be somewhat more satisfactory because it avoids the necessity of injection and can be taken easily a number of times a day. Again, however, the effect lasts only a few hours, and frequently the irritation of the nasal membranes causes a diminished absorption.

A compound solution of posterior pituitary with slow absorption and a greatly prolonged antidiuretic effect is desirable, especially if there are no side reactions. Pitressin tannate in oil, administered hypodermically to patients with diabetes insipidus, has been found to have an antidiuretic effect[421, 422, 423] which may last from 24 to 96 hours. In 17 of my cases, including eight published ones[423], 1 c.c. of pitressin tannate in oil was injected subcutaneously or intramuscularly daily for several days and then on alternate days or at longer intervals. The dose has to be adjusted according to the requirements of the individual patient. Some cases eventually required only ½ c.c. of pitressin tannate in oil every other day.

All of the cases were of idiopathic origin except one with a brain tumor. There were 12 males and 5 females. Their ages ranged from 14 to 72 years. All had had diabetes insipidus for a number of years and had been relieved of the polyuria and polydipsia with intramuscular or intranasal administration of solution of posterior pituitary except for the patient with the brain tumor. Illustrations of the effect of this drug on the fluid intake and output are shown in Fig. 22 and Fig. 23.

The hypodermic administration of 1 c.c. of pitressin tannate in oil was very effective in reducing the fluid intake and output to normal in these cases. The effect of the first injection of the drug was so evident that the subsequent 24-hour fluid intake and urine volume were normal. When injected daily, its antidiuretic effect became cumulative, and these volumes decreased to below the average normal. The antidiuretic effect usually was as obvious during the second 24 hours as it was during the first 24 hours after the injection of the drug. Consequently the frequency of the use of 1 c.c. of this medication was adjusted so that it was given every 48 or 60 hours. With this adaptation the fluid intake was near normal, and the polyuria, polydipsia and thirst completely disappeared. In the case of brain tumor the duration of action of the drug was only about 30 hours, but in this case solution of posterior pituitary had no effect. This was the only case in which the drug was needed daily. At times there have been some ampules of the drug, which did not have a maximum effect, due to some difficulty in its manufacture.

a neutralizing factor in the blood, or that there is some variation in the resistance due to allergy to pituitrin. Biggart's second case which responded to the pituitrin for the first two months and then became refractory would seem to substantiate this idea.

Resistance to pituitrin in diabetes insipidus could be studied advantageously by using Lowell's methods in investigating insulin resistance. Recently he[120] found certain variations in resistance and allergy to insulin and demonstrated that the blood contained a neutralizing factor exhibiting some characteristics of an antibody. His findings indicated also that the allergy to insulin and the resistance to insulin varied independently of each other.

In this connection Williams and Cole[120a] reported a case with diabetes insipidus in which the injection of pitressin tannate in oil did not alter the urine volume but caused a chill with a temperature of 101° F. within 30 minutes. The intradermal injection of pitressin produced a violent local allergic reaction within 30 minutes. Neither the serum nor the body cells were found to inactivate pitressin any more rapidly than in normal individuals. They concluded that there is probably a congenital anomaly of the loop of henle and the distal convoluted tubules in this patient.

Dancis and associates[468] reported a similar case of a 6-month old girl with congenital diabetes insipidus who was resistant to treatment with pitressin. They believed that the polyuria was not due to a deficient neurohypophyseal activity because the polyuria did not respond to pitressin and because large amounts of an antidiuretic substance was present in this patient's urine. They suggested that in this case the polyuria was due to a congenital anomaly of the kidney, possibly an end-organ defect, resulting in inability of the kidneys to respond to normal hormonal control.

Pitressin Tannate in Oil in the Treatment of Diabetes Insipidus

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Pitressin
1cc 4id

Pitressin Tannate in Oil
1cc daily

No Therapy

No Therapy

Fluid Intake
Urine Volume

Liters of Fluid

Days

Fig. 22. Relative effects of pitressin, pitressin tannate in oil and no treatment on the daily fluid intake and output of a patient (Mr. H.N.) with diabetes insipidus.

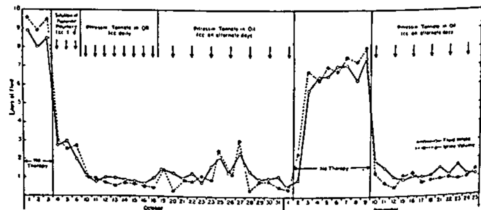


Fig. 23. Relative effects of solution of posterior pituitary, pitressin tannate in oil and no treatment on the daily fluid intake and output of a patient (Miss E.S.) with diabetes insipidus.

The patients themselves commented on the fact that pitressin tannate in oil increased their saliva and improved their appetite and digestion. Also the dryness in the mouth, which occurred even with solution of posterior pituitary, disappeared. There were no disagreeable side reactions such as local irritation, slough, pallor or intestinal cramps nor significant changes in the body weight.

In some cases I am using pitressin tannate in hydrogenated peanut oil (Parke Davis & Co.) which is made up in a disposable syringe 1 c.c. in size and contains 5 units of pitressin. The duration of effect of 1 c.c. of this preparation is usually 5 or 6 days; in one patient the effect lasted 10 to 14 days. However, in some cases a local irritation occurred at the site of injection.

The hematocrit and phenolsulfonephthalein excretion were determined in one case before, during and after treatment with pitressin tannate in oil. The phenolsulfonephthalein excretion remained the same during the various periods of observation, being approximately 68 per cent. in 130 minutes. The blood showed slight dilution as evidenced by the hematocrit of 42 per cent. without treatment and 38 per cent. during therapy.

The fluid intake and output of patients with diabetes insipidus was maintained at a normal level with pitressin tannate in oil more consistently and satisfactorily than with any other drug.

Other Methods of Treatment

As has already been stated at the beginning of this chapter, the successful treatment of the cause of diabetes insipidus is quite rare. However, when diabetes insipidus is associated with some other conditions, treatment of such a condition has resulted, at times, in an improvement or cure of the diabetes insipidus. Therapy has included surgery, x-ray, lumbar puncture, treatment of infections, diet, drugs and other miscellaneous methods. Here again the results have varied. Some of the important findings will be summarized.

In the old literature a *variety of drugs* were used in an attempt to control the polyuria and polydipsia of diabetes insipidus, particularly because pituitary extract was not available then. A list of these drugs includes valerian, asafetida, ergot[125], nitroglycerin, digitalis, antipyretics such as amidopyrine (pyramidon)[126], antipyrine[127], salicylates and seda-

tives such as opium, bromides and phenobarbitol. In general they had very little, if any, practical effect. Bromides and phenobarbitol have been used in order to enable the patient to sleep. However, with present day treatment these drugs are really not necessary.

Lumbar Puncture. – Lumbar puncture has resulted in the disappearance of the polyuria and polydipsia in rare cases[436, 437, 438]. One of my cases, a 48-year old woman, with diabetes insipidus for 15 years improved temporarily following lumbar puncture. The fluid intake and output dropped to two or three liters and returned to the original level of eight liters in nine days after lumbar puncture. I have done lumbar punctures on many other cases of diabetes insipidus without any changes in fluid intake and output.

Diet. – Various forms of diet have been suggested for the treatment of diabetes insipidus including the low-salt, low-protein and low-calorie diets. Allen and Sherrill[439] observed that restriction of protein and salt reduced thirst and polyuria in contrast to heavy protein feeding, which increased these symptoms. The restriction of the sodium chloride appeared more essential than the reduction of protein. The best results were obtained when sodium chloride was limited to less than 1 gm. daily. However, it is evident that marked curtailment in protein and salt are impractical because of their exhausting effect, particularly on the active patient. Furthermore the resultant diminution in fluid intake and output is comparatively small and does not warrant such a regimen. The same limitations are also true for the low-calorie diet.

Treatment of Diabetes Insipidus in Combination with Other Diseases

Brain Tumor. – Removal of certain brain tumors rarely results in a cure or in improvement of the polyuria and polydipsia. A review of Cushing's cases at the Peter Bent Brigham Hospital reveals that removal of a brain tumor or evacuation of a cyst may produce no variations or may aggravate the diabetes insipidus in addition to effecting some improvement and causing a temporary or permanent cure. No doubt the persistence of the diabetes insipidus after operation is due to the long continued pressure of the tumor, which damages the supraoptic hypophyseal system beyond regeneration. Four of Cushing's cases developed post-operative diabetes insipidus immediately after operation on craniopharyngeal pouch cysts. Recently Grant[123] reported complete relief of diabetes insipidus by evacuating the cysts in three out of four cases of

craniopharyngioma. On the contrary, in two other instances diabetes insipidus was a consequence of such an operation.

X-ray therapy to the pituitary and hypothalamic regions may be of value in relieving the symptoms of this disease, if the cause is a tumor, which is radio sensitive, and if the changes in the supraoptic hypophyseal tract are not beyond repair. Jones[117] and Horrax[118b] each found that diabetes insipidus was benefited in three tumor cases treated in this manner. Weinstein and Spingarn[128a] reported a case of diabetes insipidus, following a middle ear infection, which terminated after deep roentgen therapy to the pituitary region.

Irradiation with roentgen rays of the area of the hypophysis in a case of diabetes insipidus and diabetes mellitus[127] caused no effect on the excretion of urine but it did increase the excretion of sugar.

Xanthomatosis. – Various forms of treatment have been recommended for xanthomatosis including diets low in fat[129], high in calcium and vitamin D, as well as insulin injection, thyroid and parathyroid extracts. Except for x-ray therapy they have had little or no effect on the xanthomatous process and diabetes insipidus. Improvement in the xanthomatosis may result in amelioration of the polyuria and polydipsia. However, spontaneous remissions may occur in this disease as well as during any form of therapy[130, 131]. The effect of x-ray therapy in xanthomatosis seems to be local and specific. Sosman[129] showed that there was a prompt disappearance of the defects in the bones but that the improvement was least marked with regard to the exophthalmos.

Syphilis. – Certain cases of diabetes insipidus associated with syphilis may respond to antisyphilitic treatment[132]. In 1909 Ebstein[133] found that antisyphilitic treatment benefited 17 out of 23 cases of diabetes insipidus with syphilitic meningitis. Benario[134] reported either a cure or improvement with arsphenamine therapy in seven cases. Umber[135] cured with antisyphilitic treatment a patient whose Wassermann reaction was positive in the blood and negative in the spinal fluid. Schnetz and Luchner[470] obtained successful results with malarial treatment of diabetes insipidus of syphilitic origin.

One of our patients, a 36-year old woman with diabetes insipidus and syphilis, improved rapidly within two weeks after treatment with arsphenamine, mercury succinimide and potassium iodide. Another patient, a 17-year old boy, who had congenital syphilis and diabetes insipidus of two years' duration, was treated on many occasions for syphilis. The Wassermann reaction remained positive, and there was no improvement

in his diabetes insipidus. He did not respond to pituitrin therapy. However, autopsy revealed that this boy had two separate tumors, one a tumor of the third ventricle and another an adenoma of the pineal gland.

Cammidge's patient[438], a 42-year old man, with an old syphilis history and mild diabetes insipidus was given antisyphilitic treatment without benefit. Yet, the polyuria rapidly subsided after lumbar puncture. The symptoms of diabetes insipidus probably were due to parasyphilitic changes at the base of the brain which interfered with the passage of secretion of the hypophysis into cerebrospinal fluid. Withdrawal of some of the fluid, by sudden changes of pressure produced within the cerebrospinal canal, most likely broke down adhesions and opened a channel for its normal passage again to relieve the diabetes insipidus.

Pellagra. — Since polyuria and polydipsia are so frequent an accompaniment of pellagra, naturally cases of diabetes insipidus associated with pellagra should be treated as a deficiency disease with a high vitamin content in the diet, especially nicotinic acid. This form of therapy has been shown to improve the polyuria and polydipsia.

Infections. — When the origin of the disease is tuberculosis or encephalitis due to other infections, these diseases should be viewed differently from the manner in which they were in the past. With the modern methods of chemotherapy and antibiotics some of these cases, that did not respond to treatment previously, possibly may respond now.

Other Endocrine Treatment

There is a close relationship between diabetes insipidus and the general endocrine system. Certain other endocrine treatment in addition to posterior pituitary therapy has been used in an attempt to relieve the symptoms of diabetes insipidus. Other methods of endocrine therapy used in diabetes insipidus include transplantation of the pituitary gland, thyroidectomy, the administration of thiouracil, antuitrin-S, estrogens, testicular extracts and corpus luteum extract.

Transplantation of Pituitary Gland. — Experimental work on the transplantation of the pituitary gland has been reported. Hirsch and Demel[440] in 1936 implanted a human hypophysis in the abdomen of a patient with a resultant cure of the diabetes insipidus. Hirsch[441] successfully transplanted into the rectus muscle of a patient with traumatic diabetes insipidus the posterior lobe of a human hypophysis obtained from a person of the same blood group but of different sex. The polyuria

was much reduced. In further experimental work Hirsch in 1937 grafted the pituitary gland of a sheep into a young patient with transitory relief.

Azérad[110a] implanted very small fragments of posterior pituitary gland of the bull in a female patient with diabetes insipidus and obtained complete relief of the polyuria and polydipsia within one-half hour after the implantation. This relief lasted 8 to 11 days on repeated occasions. The fresh posterior lobe of the pituitary gland was cut into small particles, mixed with physiological salt solution and then injected subcutaneously through a needle 1 mm. in diameter. He also had used the hypophysis of a premature human fetus delivered by caesarean section but obtained no improvement in the diabetes insipidus. Apparently the embryo was too young.

In the case of Falta and Titze[69] the polyuria was reduced only temporarily by the implantation of two calf hypophyses in the abdominal skin of the patient.

Total Thyroidectomy in Diabetes Insipidus. – Because the thyroid gland probably plays a rôle in the regulation of the intake and output of fluids in patients with diabetes insipidus, it appeared of value to apply this knowledge clinically in the treatment of diabetes insipidus. Consequently, total thyroidectomy was performed in 1935 on three of my patients with this disease[9], aged 27, 29 and 66 years. They have been observed for the subsequent 13 years since thyroidectomy. The etiology was idiopathic in one case and of postencephalitic origin in two cases.

In the two cases of postencephalitic origin after total thyroidectomy there was a gradual decrease in the fluid intake and output. This finding is illustrated in Fig. 2 on an earlier page. In addition there was some beneficial effect on the Parkinson's disease. Thyroidectomy had no appreciable effect on the diabetes insipidus of idiopathic origin. The evidence in these cases justify the application of thyroidectomy in patients with diabetes insipidus associated with postencephalitic Parkinson's disease but not in the idiopathic type. Since these patients had total thyroidectomies performed in 1935, several reports have appeared in the literature on total or subtotal thyroidectomy in patients with diabetes insipidus.

McConnell[112] reported a case in which diabetes insipidus and thyrotoxicosis were associated with a thyroid adenoma and removal of the adenoma of the thyroid gland resulted in immediate relief of the symptoms of diabetes insipidus. On the other hand, McPhedran's[113] case of diabetes insipidus and toxic goiter showed no improvement in the polyuria after subtotal thyroidectomy. Ferro-Luzzi[114] and Findley[115] each

reported a case of diabetes insipidus in which total thyroidectomy had no appreciable effect on the polydipsia and polyuria of the disease. There was no guarantee that all the thyroid tissue was removed. However, both of their patients had syphilis which may have been a factor in their results.

Thiouracil and Propylthiouracil in Diabetes Insipidus. — Relief of polyuria in certain cases of diabetes insipidus following total thyroidectomy has led to the use of thiouracil and propylthiouracil. Astwood[116] has demonstrated that thiouracil and propylthiouracil caused a marked reduction in the basal metabolic rate and relieved hyperthyroidism by action on the thyroid gland.

In a group of four of my patients with diabetes insipidus the administration of thiouracil had no effect on the fluid intake and output in three ambulatory patients. However, there was a marked decrease in one who was a 43-year old man with diabetes insipidus for many years. He was treated in the hospital for five months. The gradual reduction of his fluid volume after the administration of .2 gm. thiouracil five times a day is shown in Fig. 24. During this period of observation his basal metabolism fell from plus 6 per cent. at the start of treatment to minus 10 per cent. His thyroid gland became slightly enlarged. There were no other marked changes. Biopsy of the thyroid gland one and four months after the starting of thiouracil showed slight hyperplastic changes.

A second patient in this group showed a striking change as a result of a similar administration of thiouracil. While there was no decrease in his fluid intake and output, the thyroid gland became considerably enlarged, increasing his neck circumference by approximately two inches. However, omission of the drug restored his neck to its normal size in two months.

Propylthiouracil, 100 milligrams three times a day, was given to four patients with diabetes insipidus for several months. In these cases there was no appreciable change in the fluid intake and output even though the basal metabolism decreased.

The appreciable effects, which the thiouracil had on the first case, may have been due to changes in the pituitary gland. Reveno[117] found that the administration of thiouracil in animals caused the disappearance of the eosinophilic elements. Furthermore, the increased basophilia in the anterior lobe of the pituitary gland simulated changes found in those subjected to thyroidectomy, where the development of so-called "thyroidectomy cells" take place.

Sex Hormones. — Meyer-Noble[118] found corpus luteum extract to be

effective in relieving the polyuria and polydipsia in a girl with delayed menstruation.

There is experimental evidence that the administration of estrogenic substance may suppress the diabetogenic and sex principles of the anterior lobe of the pituitary gland. The polyuric effect of certain extracts of the anterior lobe of the pituitary has been reported by a number of authors[410, 450], and it is believed that this gland secretes a diuretic substance. It seemed practical to determine whether the so-called diuretic principle of the anterior pituitary gland may be suppressed in a similar manner. There have appeared clinical investigations to substantiate this idea. Troisier[451] and Beltrametti[452] have injected large doses of folliculin into patients with diabetes insipidus and obtained a marked antidiuretic

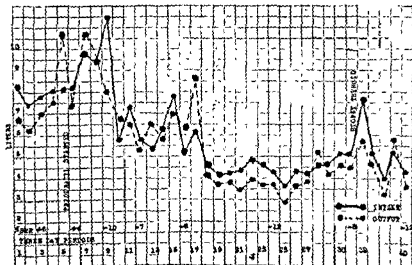


Fig. 24. The effect of thiouracil 0.2 grams five times a day on the daily fluid intake and output of a patient in the hospital for four months. Each observation period represents three days. *Patient had diabetes insipidus of idiopathic origin.* Thyroid biopsy 5 months after starting thiouracil was again followed by temporary increase in polyuria and polydipsia.

effect within several days. Omission of the folliculin resulted in a return of the polyuria. Astwood[453] also noted, following amniotin administration, a temporary improvement of the diabetes insipidus in a woman in whom menopause had been induced artificially five years previously by

reported a case of diabetes insipidus in which total thyroidectomy had no appreciable effect on the polydipsia and polyuria of the disease. There was no guarantee that all the thyroid tissue was removed. However, both of their patients had syphilis which may have been a factor in their results.

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Sex Hormones.—Meyer-Noble[118] found corpus luteum extract to be

insipidus which was permanently cured by an intercurrent attack of measles back in 1892.

Diabetes insipidus has disappeared even after the application of blisters to the chest[7].

Bee Stings. — McPhedran[413] reported that a man was cured of diabetes insipidus following 40 bee stings received all at one time.

In one patient with diabetes insipidus I injected bee venom (Lyovac, Sharp and Dohme), the equivalent of 40 stings during a period of eight days. This therapy resulted in no decrease in the fluid intake and output. I did not dare to give 40 stings at one time because the patient was allergic.

Electric Shock. — Electric shock treatment in mental disorders has been used since 1938. Ellis and Wiersma[409] studied the influence of electronarcosis on the secretory activity of the pituitary gland in guinea pigs and dogs. They found that electronarcosis in animals resulted in hypertrophy of the thyroid, adrenals and gonads. Since an increase in thyrotropic substance is found in the blood of electronarcotized dogs, they believed that the mechanism by which thyroid hypertrophy is obtained is by an increased secretion of the pituitary hormone. It is conceivable that general cortical and subcortical stimulation from passage of the current could produce direct nerve stimulation of respective endocrine organs.

The effect of electric shock treatment was studied in one of my patients, a 35-year old man with diabetes insipidus for over 16 years. He was depressed and agitated and drank much liquor. He was given 16 standard electric shock treatments in four weeks' time. During the subsequent nine months of observation there has been no improvement in the polyuria and polydipsia. If anything, there was a slight increase in the daily fluid intake and output.

Short Wave Treatment. — Drouet, Verain, Grandpierre and Pierquin[400] found that short wave treatment of the tubero-pituitary region reduced the polyuria from seven to two liters in a case of traumatic diabetes insipidus. Whether this is a matter of coincidence is a question because of the tendency to spontaneous improvement after traumatic diabetes insipidus.

Surgery in Patients with Diabetes Insipidus

Surgery may be performed on patients with diabetes insipidus without any greater risk than in the general run of cases. Preparation for

irradiation of the ovaries. Shapiro[453a] observed that the urine volume decreased 30 to 60 per cent. after the injection of large doses of estrogen (oestradiol benzoate, 10 mgm. daily for five days) in normal persons and in those with diabetes insipidus. After the omission of the drug the urine volume returned to its pre-injection level. On the basis of the fact that pregnancy improved diabetes insipidus in a patient Duvoir, Pollet and Cachin[331] administered folliculin to this patient and obtained a reduction in the volume of urine again.

I[454] treated five cases of diabetes insipidus with daily injections of 20,000 units of amniotin, the estrogenic substance prepared from the urine of pregnant mares and amniotic fluid, and found no change in their fluid intake and output. Apparently this substance did not suppress the diuretic principle of the anterior lobe of the pituitary gland. However, there appeared a definite improvement in the sugar tolerance. Such improvement has been noted by Barnes, Regan and Nelson[455] in experimental diabetes mellitus following the administration of amniotin. Collens and associates[456], however, were unable to confirm this change.

Allen and Stokes[81] reported a cure of diabetes insipidus coincident with bilateral correction of abdominal cryptorchidism in a boy following a series of 25 injections of 1 c.c. doses of antuitrin-S during a two-month period. At the end of a month after the fifteenth injection, the polyuria and polydipsia had disappeared.

The injection of antuitrin-S over a period of two months in four of my cases caused no improvement in the symptoms of diabetes insipidus. Antuitrin-S is the standard gonadotrophic factor of the anterior-pituitary-like sex hormone obtained from the urine of pregnancy.

Miscellaneous Treatment

There are reported instances in which the polyuria and polydipsia have terminated spontaneously. Of the numerous cases of diabetes insipidus, which I have followed for many years, I have never seen a case of real diabetes insipidus terminate spontaneously. However, there are cases in which intercurrent pathological conditions have caused patients to be relieved of the diabetes insipidus. For example, Strauss[8] had a case of diabetes insipidus which disappeared with the appearance of myxedema. Silvestri's[457] patient, a 20-year old youth, was relieved of diabetes insipidus when his testes descended. The polyuria had been present since the boy was four years old. Harvey[458] presented a case of diabetes

edge of the cause and mechanism of the disease and more particularly, antedate ability to manufacture the agent required to control diabetes insipidus in a form safe to give to man in a way effective in its control. With these attained, all of these other forms of treatment have become almost entirely obsolete and except for historical purposes largely may be forgotten.

Now that we know that diabetes insipidus in the words of its definition, as given on the opening page of this chapter, is due to a deficient formation of pituitary extract secreted by the posterior lobe of the pituitary, all that was necessary for adequate therapy was a knowledge of how to prepare such an extract from an available source in a form safe to give to man without losing its physiological activity. With this accomplished by the preparation of posterior pituitary extract and pitressin, treatment has become reduced to the use of these preparations as described under the heading, Treatment. Using them, diabetes insipidus can be controlled so that no longer is it a menace to health and hardly more than a minor discomfort, although in an accurate sense it is not a curable disease but only one that can be safely, comfortably and almost completely controlled. All the physician who has a patient with diabetes insipidus, really needs to know so far as control of the diabetes insipidus itself is concerned is how to use posterior pituitary extract and/or pitressin. Other methods therein discussed practically need never be used. There are but few diseases at present whose treatment is so simple and so satisfactory as is true of diabetes insipidus.

operation should be made according to the standard methods. However, it is well to give patients pituitrin before operation to control water excretion. Otherwise such individuals may become markedly dehydrated. Furthermore, if no pituitrin is given, the bladder may become markedly distended with urine. Local, spinal or general anesthesia may be used to fit the individual case.

The type of surgery performed in most of my cases has been mainly for brain tumor because of the large group of such cases in this series. It is surprising how well, in general, these patients went through the operations. Three patients had operations for acute appendicitis and recovered. Four had thyroid operations for therapy and study.

One 54-year old woman had an abdominal perineal resection for an adenocarcinoma of the rectum. She had a normal postoperative course until the seventeenth day when she died suddenly of a pulmonary embolus. Another 63-year old woman had a panhysterectomy for adenocarcinoma of the fundus of the uterus with extension to the mesosalpynx and died several days later apparently of cerebral thrombosis. A third patient, 48 years old, who had diabetes insipidus for 37 years had a hysterectomy for fibroids and made a rapid recovery after surgery.

There were also other types of surgery including deliveries, a cesarian operation, minor operations and extractions of teeth without any difficulty. Several patients had fractures due to trauma. These healed normally.

Diabetes insipidus is no contraindication to surgery and to the various forms and methods of anesthesia.

Tonsillectomy.—Winter[170] noted sudden recovery from diabetes insipidus in a 7-year old boy the day following tonsillectomy which was done under ether anesthesia. In this case the child had had diabetes insipidus for 5 months previously and a daily fluid intake of 5760 c.c. which responded to pituitrin therapy. There was no recurrence of the polyuria and polydipsia during the following year of observation. It was felt that this boy had a chronic upper respiratory infection.

Summary of Treatment

The treatment of diabetes insipidus illustrates almost perfectly the axiom that a multitude of remedies points to a woeful absence of knowledge of the cause and cure of a disease. In the preceding pages a very large number of measures, used in the past in the treatment of diabetes insipidus, have been discussed. Largely they antedate accurate knowl-

10. KAHLER, O.: Die Dauernde Polyurie als Cerebrales Herdsymptom, Zeitschr. f. Heilk, VII, 105, 1886.
11. BAILEY, P. and BREMER, F.: Experimental diabetes insipidus, Arch. Int. Med., 1921, XXVIII, 773.
12. MEYER, E.: Über Diabetes insipidus und andere Polyurien, Deutsch. Arch. f. klin. Med., 1905, LXXXIII, 1. TALLQUIST, T. W.: Untersuchungen über eimen Fall von Diabetes insipidus, Zeitsch f. klin. Med., 1903, IL, 181. SOCIN, CH.: Ueber Diabetes insipidus, Zeitsch f. klin. Med., 1913, LXXVIII, 294.
13. FINKELNBURG, R.: Über das Konzentrationsvermögen der Niere bei Diabetes insipidus nach organischen Hirnerkrankungen, Deutsch. Arch. f. klin. Med., 1910, C, 33. FITZ, R.: A case of diabetes insipidus, Arch. Int. Med., 1914, XIV, 706.
14. MAGNUS, R. and SCHÄFER, E. A.: The action of pituitary extracts upon the kidney, Jour. Physiol., 1901, XXVII, Proceedings p. IX.
15. SCHÄFER, E. A. and HERRING, P. T.: The action of pituitary extracts upon the kidney, Proceedings Roy. Soc., London, 1905-06, Series B, LXXVII, 571.
16. FRANK: Ueber Diabetes insipidus als Zeichen gesteigerte Funktion des Hinterlappen der Hypophysis, Berlin. klin. Wochnschr., 1910, XLVII, 1257.
17. FUTCHER, T. B.: The etiology and treatment of diabetes insipidus, Ann. Int. Med., 1931-32, V, 566.
18. GOETSCH, E., CUSHING, H. and JACOBSON, C.: Carbohydrate tolerance and the posterior lobe of the hypophysis cerebri, Bull. Johns Hopkins Hosp., 1911, XXII, 165.
19. CUSHING, H.: Concerning diabetes insipidus and the polyurias of hypophyseal origin, Boston Med. and Surg. Jour., 1913, CLXVIII, 901.
20. FRANK, E.: Ueber Beziehungen Hypophyse zum Diabetes insipidus, Berlin. klin. Wochnschr., 1912, XLIX, 393.
21. SIMMONDS, M.: Ueber sekundare Geschwülste des Hirnanhangs und ihre Beziehungen zum Diabetes insipidus, München. med. Wochnschr., 1914, LXI, 180.
22. von den VELDEN, R.: Die Nierenwirkung von Hypophysenextrakten beim Menschen, Berlin. klin. Wochnschr., 1913, L, 2083.
23. FARINI, A.: Hypophyseal opotherapy in diabetes insipidus, Gazz. d. Osp., 1913, XXXIV, 1135, abstracted Brit. Med. Jour, 1913, II, 76.
24. CAMUS, J. and ROUSSY, G.: Hypophysectomie et polyurie expérimentales, Compt. rend. Soc. de biol., 1913, LXXV, 483. Diabète insipide expérimental et opthérapie hypophysaire, ibid., 1920, LXXXIII, 1578. Experimental researches on the pituitary body:

BIBLIOGRAPHY

1. GALEN, C.: Claudii Galeni Opera Omnia, Editionem Curavit, D.C.G. Kühn, VIII, 394, Lipsiae, Prostat in Officina Libraria Car. Cnoblochii, 1824.
2. ARETAEUS, THE CAPPADOCIAN: The Extant Works of Aretaeus, the Cappadocian, Edited and Translated by Francis Adams, London, The Sydenham Society, Book II, Chapter II, p. 339, printed by Wertheimer and Co., London, 1856.
3. WILLIS, SIR THOMAS: Pharmaceutice Rationalis sive Diatriba de Medicamentorum Operationibus in Humano Corpore, Sectio IV, Caput III, De Diuresinima eiusque remedio & speciatim de Diabete, Hagae-Comitis, Ex Officinâ Arnaldi Leers, Bibliopolae, p. 172, 1674. Pharmaceutice Rationalis sive Diatriba de Medicamentorum Operationibus in Humano Corpore, Sectio IV, Caput III, de Diuresinima eiusque remedio & speciatim de Diabete, p. 67, Amsterdam, Apud Henricum Wetstenium: Dr. Willis's Practice of Physick, being the whole WORKS of that Renowned and Famous Physician, Section on Pharmaceutice Rationalis, Part I, p. 71, London, printed for T. Dring, C. Harper, and F. Leigh, 1684.
4. CULLEN, W.: Ansfangsgründe der praktischen Arzneykunst, p. 566, Caspar Fritsch, Dritter Band, Leipsig, 1789.
5. BELLOT, M. M. and BROUGNIART: Report made to the Philomatical Society relative to a woman who drinks a great quantity of water, in Simmons's Medical Facts and Observations, II, 87, J. Johnson, London, 1792.
6. FRANK, JOHANN PETER: Grundsätze über die Behandlung der Krankheiten des Menschen zu akademischen Vorlesungen bestimmt, Funfter Theil, von den Ausflüssen (Profluvia) Mannheim, Schwan und Goss, p. 34, 1797, I Ordnung, II Geschlecht, Harnruhr: FRANK, JOANNE PETRO: De Curandis Hominum Morbis Epitome Praelectionibus Academicis Dictata, Classio Quinta, Profluvia Florentiae, Apud Coen et Socios, 1832, Ordo I, Genus II, p. 25.
7. WILLIS, ROBERT: Urinary diseases and their treatment, Sherwood, Gilbert and Piper, London, 1838, p. 2.
8. BERNARD, C.: Leçons de Physiologie Expérimentale, Tome 1, Leçon Dix-Huitième, p. 345, 27 Fevrier, 1855, J. B. Baillière et Fils, Paris, 1855.
9. ECKHARD, C.: Die Stellung der Nerven beim künstlichen Diabetes Beiträg, z. Anatomie u. Physiologie, 1869, IV, 1. Untersuchungen über Hydrurie, *Ibid.*, 1869, IV, 153. Untersuchungen über Hydrurie, *Ibid.*, 1870, V, 147. Untersuchungen über Hydrurie, *Ibid.*, 1872, VI, 51.

Physiol., 1935, CXII, 481. Experimental diabetes insipidus: its relation to the anterior and posterior lobes of the pituitary, Am. Jour. Physiol., 1934, CX, 124.

37a. BELLOWS, R. T. and Van WAGENEN, W. P.: The relationship of polyuria and polydipsia in diabetes insipidus: a study of experimental diabetes insipidus in dogs with and without esophageal fistulae, Jour. Nervous and Mental Disease, 1938, LXXXVIII, 417.

38. GREINAR, A. and PODHRADSZKY, L.: Kidney function in diabetes insipidus, Lancet, 1947, II, 498. SAMAAN, A.: The effect of the pituitary (posterior lobe) extract upon the urinary flow in non-anesthetized dogs, Jour. Physiol., 1935, LXXXV, 37. HANDOVSKY, H. and SAMAAN, A.: Effet des extraits posthypophysaires sur le débit sanguin rénal et sur la diurèse des chiens narcotisés, Compt. rend., Soc. de Biol., 1936, CXXII, 122. Observations on the renal circulation and secretion in the dog with special reference to the effect of pituitary (posterior lobe) extract, Jour. Physiol., 1937, LXXXIX, 14.

39. SCHMITZ, H. L.: The mechanism of human diabetes insipidus, Jour Clin. Invest., 1937, XVI, 675.

40. WHITE, H. L. and HEINBECKER, P.: Hypophyseal influences in renal function and water exchange in the dog, Am. Jour. Physiol., 1938, CXXIII, 213. Observations on inulin and diodrast clearances and on renal plasma flow in normal and hypophysectomized dogs, Am. Jour. Physiol., 1940, CXXX, 464. Observations on creatinine and urea clearances, on responses to water ingestion and on concentrating power of kidneys in normal, diabetes insipidus and hypophysectomized dogs, Am. Jour. Physiol., 1938, CXXIII, 566. WHITE, H. L., HEINBECKER, P. and ROLF, D.: Effects of hypophysectomy on some renal functions, Proceed. Soc. Exper. Biol. and Med., 1941, XLVI, 44.

41. WINER, N. J.: Renal function in diabetes insipidus, Arch. Int. Med., 1942, LXX, 61.

42. STARLING, E. H. and VERNEY, E. B.: The secretion of urine as studied on the isolated kidney, Proceed. Roy. Soc., London, s. B., 1925, XCVII, 321.

43. JANSSEN, S.: Ueber zentrale Wasserregulation und Hypophysenantidiurese, Arch. f. exper. Path. u. Pharmakol., 1928, CXXXV, 1.

44. VERNEY, E. B.: The secretion of pituitrin in mammals, as shown by perfusion of the isolated kidney of the dog, Proceed. Roy. Soc., London, s. B., 1926, XCIX, 487. Die Wasserausscheidung der Säugetierniere und ihre physiologische Regulation, Arch. f. exper. Path. u. Pharmakol., 1936, CLXXXI, 23. KLISIECKI, A., PICKFORD, M., ROTHSCHILD, P. and VERNEY, E. P.: The absorp-

Diabetes insipidus, glycosuria, and those dystrophies considered as hypophyseal in origin, Endocrinology, 1920, IV, 507.
25. ERDHEIM, J.: Ueber Hypophysengangsgeschwülste und Hirncholesteotome, Sitzungsb. d. k. akad. d. Wissensch. Math-naturw., CL, 1904, CXIII, 537.
26. CHRISTIAN, H. A.: Defects in membranous bones. Exophthalmos and diabetes insipidus; an unusual syndrome of dyspituitrism; a clinical study, in Contributions to medical and biological research, I, 391, Dedicated to Sir William Osler, Paul B. Hoeber, New York, 1919.
27. ELMER, A. W., KEDZIERSKI, J. and SCHEPS, M.: Ein Fall von Diabetes insipidus verursacht eine Metastase eines Hypernephrons in Zwischenhirn, Beiträg zur Pathogenese des Diabetes insipidus, Wien, klin. Wochnschr., 1928, XLI, 591.
28. GREVING, R.: Beiträge zur Anatomie der Hypophyse und ihren Funktion: 1. Eine Faserverbindung zwischen Hypophyse und Zwischenhirnbasis (Tr. supraoptico-hypophyseus), Deutsch. Zeitschr. f. Nervenh., 1926, LXXXIX, 179.
29. PINES, I. L.: Über die Innervation der Hypophysis cerebri, II. Mitt. Ueber die Innervation des Mittel und Hinterlappens der Hypophyse, Zeitschr. f. d. ges. Neurol. u. Psychol., 1925-26, C, 123.
30. ZADEK, E.: Die Beziehungen zwischen Anatomie und Klinik des Diabetes insipidus, Zeitschr. f. klin. Med., 1927, CV, 603.
31. BLOTNER, H. and CUTLER, E. C.: Total thyroidectomy in the treatment of diabetes insipidus, Jour. Am. Med. Assoc., 1941, CXVI, 2739.
32. ROGOWITSCH, N.: Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse, Beiträg. z. path. Anat. u. z. allg. Path., 1889, IV, 453.
33. FISHER, C., INGRAM, W. R. and RANSON, S. W.: Diabetes insipidus and the neuro-hormonal control of water balance; a contribution to the structure and function of the hypothalamico-hypophyseal system, Edwards Brothers Inc., Ann Harbor, Michigan, 1938.
34. FRIEDGOOD, H. B.: Endocrine functions of the hypophysis, p. 811, Oxford Medicine, Vol. III, chapt. XIV, Oxford University Press, Inc., New York, 1945.
35. CANNON, W. B.: The physiological basis of thirst, Proceed. Roy. Soc. London, s. B., 1917-18, XC, 283. Hunger and Thirst, Murchison's Psychology, Clark University Press, Worcester, Mass., 1934.
36. HOLMES, J. H. and GREGERSEN, M. I.: Origin of thirst in diabetes insipidus, Am. Jour. Med., 1948, IV, 503.
37. RICHTER, C. P.: Experimental diabetes insipidus, Brain, 1930, LIII, 76. The primacy of polyuria in diabetes insipidus, Am. Jour.

Physiol., 1935, CXII, 481. Experimental diabetes insipidus: its relation to the anterior and posterior lobes of the pituitary, Am. Jour. Physiol., 1934, CX, 124.

37a. BELLOWS, R. T. and Van WAGENEN, W. P.: The relationship of polyuria and polydipsia in diabetes insipidus: a study of experimental diabetes insipidus in dogs with and without esophageal fistulae, Jour. Nervous and Mental Disease, 1938, LXXXVIII, 417.

38. GREINAR, A. and PODHRADSZKY, L.: Kidney function in diabetes insipidus, Lancet, 1947, II, 498. SAMAAN, A.: The effect of the pituitary (posterior lobe) extract upon the urinary flow in *non-anesthetized dogs, Jour. Physiol., 1935, LXXXV*, 37. HANDOVSKY, H. and SAMAAN, A.: Effet des extraits posthypophysaires sur le débit sanguin rénal et sur la diurèse des chiens narcotisés, Compt. rend., Soc. de Biol., 1936, CXXII, 122. Observations on the renal circulation and secretion in the dog with special reference to the effect of pituitary (posterior lobe) extract, Jour. Physiol., 1937, LXXXIX, 14.

39. SCHMITZ, H. L.: The mechanism of human diabetes insipidus, Jour. Clin. Invest., 1937, XVI, 675.

40. WHITE, H. L. and HEINBECKER, P.: Hypophyseal influences in renal function and water exchange in the dog, Am. Jour. Physiol., 1938, CXXIII, 213. Observations on inulin and diodrast clearances and on renal plasma flow in normal and hypophysectomized dogs, Am. Jour. Physiol., 1940, CXXX, 464. Observations on creatinine and urea clearances, on responses to water ingestion and on concentrating power of kidneys in normal, diabetes insipidus and hypophysectomized dogs, Am. Jour. Physiol., 1938, CXXIII, 566. WHITE, H. L., HEINBECKER, P. and ROLF, D.: Effects of hypophysectomy on some renal functions, Proceed. Soc. Exper. Biol. and Med., 1941, XLVI, 44.

41. WINER, N. J.: Renal function in diabetes insipidus, Arch. Int. Med., 1942, LXX, 61.

42. STARLING, E. H. and VERNEY, E. B.: The secretion of urine as studied on the isolated kidney, Proceed. Roy. Soc., London, s. B., 1925, XCVII, 321.

43. JANSSEN, S.: Ueber zentrale Wasserregulation und Hypophysenantidiurese, Arch. f. exper. Path. u. Pharmakol., 1928, CXXXV, 1.

44. VERNEY, E. B.: *The secretion of pituitrin in mammals*, as shown by perfusion of the isolated kidney of the dog, Proceed. Roy. Soc., London, s. B., 1926, XCIX, 487. Die Wasserausscheidung der Saugetierniere und ihre physiologische Regulation, Arch. f. exper. Path. u. *Pharmakol., 1936*, CLXXXI, 23. KLISIECKI, A., PICKFORD, M., ROTHSCHILD, P. and VERNEY, E. P.: The absorp-

tion and excretion of water by the mammal: the relation between absorption of water and its excretion by the innervated and denervated dog, Proceed. Roy. Soc., London, s. B., 1933, CXII, 496. THEOBALD, G. W.: The repetition of certain experiments on which Molitor and Pick base their water centre hypothesis and the effect of afferent nerve stimuli on water diuresis, Jour. Physiol., 1934, CCXLIII, 81.

45. ADDIS, T., SHEVKY, A. F. and BEVIER, G.: The regulation of renal activity: VII. The balance between the regulation of adrenalin and by pituitrin, Am. Jour. Physiol., 1918, XLVI, 129.

46. POULSSON, L. T.: Ueber die Wirkung des Pituitrins auf die Wasserausscheidung durch die Niere, Zeitschr. f. d. ges. exper. Med., 1930, LXXI, 577.

47. GERSCH, I. and STIEGLITZ, E. J.: Histochemical studies of the mammalian kidney: 1. The glomerular elimination of ferrocyanide in the rabbit and some related problems, Anat. Rec., 1934, LVIII, 349.

48. GERSCH, I.: Reabsorption of water during pituitary anti-diuresis, Jour. Pharmacol. and Exper. Therap., 1934, LII, 231.

49. BURGESS, W. W., HARVEY, A. M. and MARSHALL, E. K., Jr.: The site of antidiuretic action of pituitary extract, Jour. Pharmacol. and Exper. Therap., 1933, XLIX, 237.

50. Van DYKE, H. B.: The Physiology and Pharmacology of the Pituitary Body, The University of Chicago Press, Chicago, Illinois, 1936.

51. STEHLE, R. L.: The constituent of the posterior lobe of the pituitary gland responsible for the antidiuretic action, Jour. Pharmacol. and Exper. Therap., 1934, LI, 146. Der antidiuretisch wirkende Anteil des Hypophysenhinterlappens, Arch. f. exper. Path. u. Pharm., 1934, CLXXV, 466.

52. GEILING, E. M. K.: The posterior hypophysis, Jour. Am. Med. Assoc., 1935, CIV, 738.

53. GERSCH, I.: The structure and function of the parenchymatous glandular cells in the neurohypophysis of the rat, Am. Jour. Anat., 1939, LXIV, 407.

54. BROOKS, C. McC. and GERSCH, I.: Pericellular nerve terminations in the pars nervosa and pars distalis of the rat's pituitary, Anat. Rec., 1938, LXX (Suppl. 3), 10.

55. GEILING, E. M. K. and LEWIS, M. R.: Further information regarding the melanophore hormone of the hypophysis cerebri, Am. Jour. Physiol., 1935, CXIII, 534.

56. VERNEY, E. B.: The secretion of pituitrin in mammals as shown by perfusion of the isolated kidney in the dog, Proceed. Roy. Soc., London, 1926, XCIX, 487. Goulstonian lectures on polyuria. 1.

Polyuria associated with pituitary dysfunction, Lancet, 1929, CCXVI, 539.
57. VERNEY, E. B.: Absorption and excretion of water. The antidiuretic hormone, The Lancet, 1946, Nov. 23 (p. 739) and Nov. 30 (p. 781).
57a. VERNEY, E. B.: *The antidiuretic hormone and the factors which determine its release*, Proceed. Roy. Soc., B., 1947, CXXXV, 25.
58. KLISIECKI, A., PICKFORD, M., ROTHSCHILD, P. and VERNEY, E. P.: The absorption and excretion of water by the mammal: the relation between absorption of water and its excretion by the innervated and denervated dogs, Proceed. Roy. Soc., London, s. B., 1933, CXII, 496.
59. GILMAN, A., and GOODMAN, L.: Secretion of antidiuretic hypophyseal hormone in response to the need for renal water conservation, Science, *1936, LXXXIV, 24. The secretory response of the* posterior pituitary to the need for water conservation, Jour. Physiol., 1937, XC, 113.
60. SHANNON, J. A.: The control of the renal excretion of water, The rate of liberation of the posterior pituitary antidiuretic hormone in the dog, Jour. Exper. Med., 1942, LXXVI, 387.
61. VON HANN, F.: Ueber die Bedeutung der Hypophysenveranderungen bei Diabetes insipidus, Frankf. Zeitschr. f. Path., 1918, XXI, 337.
61a. HIRSCH, O.: *Diabetes insipidus, Wien. klin.* Wochnschr., 1931, XLIV, 1387. Personal communication.
62. CUSHING, H.: Concerning diabetes insipidus and the polyurias of hypophyseal origin, Boston Med. and Surg. Jour., 1913, CLXVIII, 901. RICHTER, C. P.: Experimental diabetes insipidus: its relation to the anterior and posterior lobes of the hypophysis, Am. Jour. Physiol., 1934, CX, 439. PENCHARZ, R. I., HOPPER, J., Jr. and RYNEARSON, E. H.: Water metabolism of the rat following removal of the anterior lobe of the hypophysis, Proceed. Soc. Exper. Biol. and Med., 1936, XXXIV, 14.
63. KELLER, A. D.: Hypophyseal thyrotropic mechanism essential for occurrence of diabetes insipidus in its maximal force, Proceed. Soc. Exper. Biol. and Med., 1937, XXXVI, 787.
64. BEST, C. H. and TAYLOR, N. B.: *The Physiological Basis of Medical Practice*, p. 740, The Williams and Wilkins Company, Baltimore, 1945.
65. RICHTER, C. P. and WISLOCKI, G. B.: Anatomical and behavior changes produced in the rat by complete and partial extirpation of the pituitary gland, Am. Jour. Physiol., 1930, XCV, 481.

66. TEEL, H. M. and CUSHING, H.: Studies on the physiological properties of the growth promoting extracts in the anterior hypophysis, Endocrinology, 1930, XIV, 157. TEEL, H. M.: Diuresis in dogs from neutralized alkaline extracts of the anterior hypophysis, Jour. Am. Med., Assoc., 1929, XCIII, 760.
67. BARNES, B. O., REGAN, J. F. and BUENO, J. G.: Is there a specific diuretic hormone in the anterior pituitary?, Am. Jour. Physiol., 1933, CV, 559. BIASOTTI, A.: Thyroïde et action diurétique de l'extrait antéhypophysaire, Compt. rend. Soc. de Biol., 1934, CXV, 329. GAEBLER, O. H.: Some effects of anterior pituitary extracts on nitrogen metabolism, water balance and energy metabolism, Jour. Exper. Med., 1933, LVII, 349. WHITE, H. L. and HEINBECKER, P.: Pituitary regulation of water exchange in the dog and monkey, Am. Jour. Physiol., 1937, CXVIII, 276.
67a. HARRIS, G. W.: Neural control of the pituitary gland, Phys. Reviews, 1948, XXVIII, 139.
68. HOFMEISTER, F.: Zur Physiologie der Schilddrüse, Fortschr. d. Med., 1892, X, 81.
69. GLEY, E.: Recherches sur fonction de la glande thyroïde, Arch. de Physiol., 1892, XXIV, 311.
70. PISENTI, G. and VIOLA, G.: Beiträg zur normalen und pathologischen Histologie der Hypophyse und bezüglich der Verhältnisse zwischen Hirnanhand und Schilddrüse, Centralbl. f. die med. Wissensch., 1890, XXVIII, 450.
71. SCHÖNEMANN, A.: Hypophysis und thyroidea, Virchow's Arch. f. path. Anat., 1892, CXXIX, 310.
72. HERRING, P. T.: The effects of thyroidectomy on the mammalian pituitary, Quart. Jour. Exper. Physiol., 1908, I, 281.
73. CORONEDI, G.: Recherches comparatives sur l'action des dieurétiques et de l'extrait thyréoidien sur le rein du chien thyréoïdectomisé, Arch. ital. de Biol., 1909, LII, 336.
74. BARNES, B. O., REGAN, J. F. and BUENO, J. G.: Is there a specific diuretic hormone in the anterior pituitary? Am. Jour. Physiol., 1933, CV, 559.
75. BIASOTTI, A.: Tiroides y acción diurética del extract de lóbulo anterior de la hipófisio, Rev. Soc. Argent. de Biol., 1933, IX, 409.
76. MARINE, D. and ROSEN, S. H.: Cited by Marine. MARINE, D.: The physiology and principal interrelations of the thyroid, Jour. Am. Med. Assoc., 1935, CIV, 2250.
77. MAHONEY, W. and SHEEHAN, D.: The effects of total thyroidectomy on experimental diabetes insipidus in dogs, Am. Jour. Physiol., 1935, CXII, 250. FISHER, C. and INGRAM, W. R.:

Effect of feeding of thyroid or salt and thyroidectomy on fluid exchange of cats with diabetes insipidus, Arch. Int. Med., 1936, LVIII, 117.

78. STRAUSS, L.: Uebergang eines Falles von Diabetes insipidus in Myxödem, Deutsch. med. Wochnschr., 1920, XLVI, 939.

79. BLOTNER, H. and CUTLER, E. C.: Total thyroidectomy in the treatment of diabetes insipidus, Jour. Am. Med. Assoc., 1941, CXVI, 2739.

80. DEL CASTILLO, E. B. and PASQUALINI, R. Q.: Diabetes insipida en el curso del ambarazo y después de las castración, Medicina, Buenos Aires, 1942, II, 335.

81. ALLEN, A. A. and STOKES, J. S.: Cure of diabetes insipidus coincident with bilateral correction of abdominal cryptorchidism by gonadotropic factor from pregnancy urine, Jour. Am. Med. Assoc., 1936, CVI, 780.

82. SCHLOTTHAUER, C. F.: Diabetes insipidus in a bovine male, Jour. Am. Vet. Med. Assoc., 1935, XXXIX, 673.

83. HAMILTON, J. B.: Personal communication.

84. GOTTLIEB, K.: Die Pathologie der Dystrophia adiposogenitalis, Ergebn. d. allgem. Path. u. path. Anat., 1921, XIX, 575.

85. LICKINT, F.: Ist der Diabetes insipidus eine genitohypophysare Erkrankung? Deutsch. med. Wochnschr., 1934, LX, 1672.

86. ROTHMANN, H.: Zur Behandlungen des Diabetes insipidus mit Hodenextrakt, Med. Klin., 1925, XXI, 1537.

87. KAIRIUKSTIS, V.: Organtherapie bei Diabetes insipidus, Med. Klin., 1925, XXI, 1136.

88. INGRAM, W. R. and WINTER, C. A.: The effects of adrenalectomy upon the water exchange of cats with diabetes insipidus, Am. Jour. Physiol., 1938, CXXII, 143.

89. RAGAN, C., FERREBEE, J. W., PHYFE, P., ATCHLEY, D. W. and LOEB, R. F.: A syndrome of polydipsia and polyuria induced in normal animals by desoxycorticosterone acetate, Am. Jour. Physiol., 1940, CXXXI, 73.

90. SILVETTE, H. and BRITTON, S. W.: Renal function in oppossum and mechanism of cortico-adrenal and post-pituitary action, Am. Jour. Physiol., 1938, CXXIII, 630. Theory of cortico-adrenal and post-pituitary influence on kidney, Science, 1938, LXXXVIII, 150. BRITTON, S. W. and COREY, E. L.: Antagonistic adrenal and pituitary effects on body salts and water, Science, 1941, XCIII, 405. COREY, E. L. and BRITTON, S. W.: Antagonistic action of desoxycorticosterone and post-pituitary extract on chloride and water balance, Am. Jour. Physiol., 1941, CXXXIII, 511.

91. MULINOS, M. G., SPINGARN, C. L. and LOJKIN, M. E.: Diabetes insipidus-like conditions produced by small doses of desoxycorticosterone acetate in dogs, Am. Jour. Physiol., 1941, CXXXV, 102.
92. WINTER, C. A. and INGRAM, W. R.: Observations on the polyuria produced by desoxycorticosterone acetate, Am. Jour. Physiol., 1943, CXXXIX, 710.
93. ANDERSON, J. A. and MURLIN, W. R.: Antagonism of pitressin and adrenal cortical extract in human diabetes insipidus, Jour. Pediatrics, 1942, XXI, 326.
94. SHELLING, D. H.: The Parathyroids in Health and Disease, p. 92, C. V. Mosby Company, St. Louis, 1935.
95. HARE, K.: Water metabolism: neurogenic factors, in the hypothalamus and central levels of autonomic functions, Proceed. Assoc. Research in Nervous and Mental Disease, Res. Publ. Assoc. Nerv. Ment. Dis., Williams & Wilkins Co., Baltimore, 1940, XX, 416.
GERSCH, I.: Water metabolism: endocrine factors, Ibid. p. 436.
BARBOUR, H. G.: Hypothalamic control of water movement in response to environmental temperature, Ibid., p. 449.
96. STAEMMLER, M.: Diabetes insipidus und Hypophyse, Ergebn. d. allgem. Path. u. path. Anat., 1932, XXVI, 59.
97. FULTON, J. F.: Harvey Cushing, a Biography, p. 366, Charles C. Thomas, Springfield, Illinois, 1946.
98. BERBLINGER, W.: Diabetes insipidus und Tumor in der Hypophyse, Verhandl. d. deutsch. path. Ges., 1913, XVI, 272.
99. GIERKE, E. von: Hypophysis und Epiphysis bei diabetes insipidus, Verhandl. d. deutsch. path. Ges., 1914, XVII, 200.
100. SEKIGUCHI, S.: Hypophyseal disorder in mammary cancer and its relation to diabetes insipidus, Ann. Surg., 1916, LXIII, 297.
101. MARAÑON, G.: Diabetes insipidus as a hypopituitary syndrome, Endocrinology, 1921, V, 159.
102. TAKAO, T.: Zur Frage des Zwischenhirn-Hypophysenproblems, Virchow's Arch. f. path. Anat., 1926, CCLXII, 124.
103. KARY, C.: Pathologische-anatomische und experimentelle Untersuchungen zur Frage des Diabetes insipidus, Virchow's Arch. f. path. Anat., 1924, CCLII, 734.
104. PINES, I. L.: Ueber die Innervation der Hypophysis cerebri, J. f. Psychol. u. Neurol., 1925, XXXII, 80.
105. GREVING, R.: Beitrag zur Innervation der Hypophyse, Klin. Wochnschr., 1925, IV, 2181.
106. KIYONO, H.: Ueber Zwischenhirnveränderungen bei Diabetes insipidus, Virchow's Arch. f. path. Anat., 1925, CCLVII, 477.

107. FUTCHER, T. B.: Diabetes insipidus and lesions of the midbrain. Report of a case due to metastatic tumor of the hypothalamus, Am. Jour. Med. Sci., 1929, CLXXVIII, 837.
108. DESANTO, D. A.: So-called functional hypopituitarism: pathologic findings and report of a case, Arch. Neurol. and Psychiat., 1934, XXXI, 134.
109. BIGGART, J. H.: Diabetes insipidus, Brain, LVIII, 86. Diabetes insipidus. The site of formation of the antidiuretic hormone, Edinburgh Med. Jour., 1936, XLIII, 417.
110. STRINGER, S. W.: Diabetes insipidus associated with pinealoma transplant in the tuber cinereum, Yale Jour. Biol. and Med., 1934, VI, 375. FRIEDMAN, E. D. and PLAUT, A.: Tumor of the pineal gland (pinealocytoma) with meningeal and neural metastases, Arch. Neurol. and Psychiat., 1935, XXXIII, 1324. DAVISON, C. and SELBY, N. E.: Hypothermia in cases of hypothalamic lesions, Arch. Neurol. and Psychiat., 1935, XXXIII, 570.
111. FINK, E. B.: Diabetes insipidus. A clinical review and analysis of necropsy reports, Arch. Path., 1928, VI, 102. A case of diabetes insipidus associated with syphilis of the hypophysis, Endocrinology, 1926, X, 317.
112. BERNARD, C.: Leçons sur les propietés physiologiques et les altérations pathologiques des liquides de l'organisme, vol. 2, Paris, 1859.
113. CAMUS, J. and ROUSSY, G.: Diabète insipide et polyurie dite hypophysaire, Presse méd., 1914, XXII, 517. Experimental researches on the pituitary body, Endocrinology, 1920, IV, 507.
114. PARSONS, R. J.: The pituitary gland and its relation to age, hypertension and pathological processes: a study of 107 unselected pituitaries, p. 366, Medical papers dedicated to Henry Asbury Christian, Waverly Press, Inc., Baltimore, 1936.
115. CUSHING, H. and MARTIN, P.: Primary gliomas of chiasm and optic nerves in their intracranial portion, Arch. Ophth., 1923, LII, 209.
116. MARTIN, J. and DAVIS, L.: Syndrome of destruction of the pineal gland: experimental and clinical observations, Arch. Int. Med., 1941, LXVII, 1119.
116a. HORRAX, G. and WYATT, J. P.: Ectopic pinealomas in chiasmal region: report of three cases, Jour. Neurol., 1947, IV, 309.
116b. HORRAX, G.: The role of pinealomas in the causation of diabetes insipidus, Ann. Surg., 1947, CXXVI, 725.
117. JONES, G. M.: Diabetes insipidus. Clinical observations in 42 cases, Arch. Int. Med., 1944, LXXIV, 81.

118. NONNE, M.: Hypophysiserkrankungen, Münch. med. Wochnschr., 1916, LXIII, 835. Syphilis und Nervensystem, p. 241, S. Karger, Berlin, 1915.
119. ROSENBLOOM, J.: Control of polyuria in a case of diabetes insipidus by means of hypophyseal extract, Jour. Am. Med. Assoc., 1918, LXX, 1292.
120a. VON HOESSLIN, R.: Tumor der Epiphysis cerebri. Diabetes insipidus. Oculomotoriuskernlähmung, Münch. med. Wochnschr., 1896, XLIII, 292.
120b. WENTZLER, E.: Ein Fall von Carcinom der Hypophyse bei 9-jährigem Knaben, Monatschr. f. Kinderh., 1937, LXIX, 86.
121. MOFFETT, R. D.: Craniopharyngeal pouch cyst arising from pituitary body: operation with recovery, Am. Jour. Dis. Child., 1926, XXXII, 89.
122. CUSHING, H.: Pituitary Body and its Disorders. J. P. Lippincott Co., Philadelphia, 1912. Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Charles C. Thomas, Springfield, Illinois, 1932.
123. DESBUQUOIS, G.: Sur un cas de lymphogranulamatose maligne compliquée de diabète insipide, Bull. et Mém. Soc. méd. d. Hôp. de Paris, 1935, LI, 1355.
124. OPPENHEIM: In Nothnagel: Die Syphilitischen erkrankungen des Gehirns, Speziellen Pathologie und Therapie, Vienna, 1896, IX, 53.
125. DROUET, P. L. and HAMEL: Diabète insipide chez un hérédosyphilitique, Rev. méd. de l'Est, 1931, LIX, 661.
126. DEMME: Ein Fall von Diabetes insipidus, abstracted Jahrb. f. Kinderh., 1879, XIV, 437.
127. ZENKER, F.: Diabetes insipidus und Trauma, W. Nitsche, Weissenfels, 1919.
127a. PICKLES, W.: Disturbances of metabolism with head injuries, New Eng. Jour. Med., 1947, CCXXXVI, 858.
128. KINDWALL, J. A. and CLEVELAND, D.: Pre-frontal lobotomy, fifteen patients before and after operation, Am. Jour. Psychiat., 1945, CI, 749. ZIEGLER, L. H. and OSGOOD, C. W. A.: Edema and trophic disturbances of the lower extremities complicating prefrontal lobotomy, Arch. Neurol. and Psychiat., 1945, LIII, 262.
129. RISER, LAZORTHE, COUADAU and GÉRAUD: Diabète insipide par polydipsie primaire au cours de l'ablation d'un kyste optochiasmique récidevant, Bull. et Mém. Soc. méd. d. Hôp., Paris, 1945, LXI, 414.
130. KOURILISKY, R., DAVID, M., SICARD, J. and GALEY, J. J.: Diabète insipide posttraumatique—cessation subite de la soif au

cours de l'ouverture d'un kyste arachnoidien de la région opto-chiasmique-guérison, Rev. Neurol., 1942, LXXIV, 264.

131. WARKANY, J. and MITCHELL, A. G.: Diabetes insipidus in children. A critical review of etiology, diagnosis and treatment with reports of four cases, Am. Jour. Dis. Child., 1939, LVII, 603.

132. FINDLAYSON, J.: Diabetes insipidus with great enlargement of the bladder, Glasgow Med. Jour., 1881, XV, 17.

133. KÜLZ, in GERHARDT, C.: Handbuch der Kinderkrankheiten, XIII, 1, H. Laupp, Tubingen, 1887-1893.

134. BLATT, M. L. and GREENGARD, J.: Diabetes insipidus. Report of a case in a child, Arch. Pediat., 1926, XLIII, 811.

135. GAYLER: Ueber das Zustandekommen der Wachstumsstörungen bei Diabetes insipidus des Kindes, Monatschr. f. Kinderh., 1921, XXI, 356.

136. TURNER, H. H.: Diabetes insipidus: report of a case in a child, Arch. Pediat., 1928, LXV, 433.

137. DANERI, J.: Diabetes insipida, Rev. Chilena de Pediat., 1934, V, 306.

138. WHITTLE: Cited by EICHORN, G.: Ueber Diabetes insipidus in Kindersalter, Jahrb. f. Kinderh., 1896, XLII, 44.

139. FLANDIN, C., POUMEAU-DELILLE, G., PUECH and AUZÉPY, P.: Diabète insipide et obésité avec vergetures par atteinte infundibulo-tubérienne d'origine ourlienne, Bull. et Mém. Soc. méd. d. Hôp. de Paris, 1935, LI, 1244.

140. SALMI, T.: Diabetes insipidus complicating chicken pox, Duodecim, 1936, LII, 304.

141. ROEHM, H. R.: Postvaccinal encephalitis associated with diabetes insipidus, Am. Jour. Dis. Child., 1932, XLIV, 1293.

142. DAVIS, J. N. P.: Diabetes insipidus and obesity in an Itesot leper child, East African Medical Journal, 1946, XXXIII, 43.

143. MUWAZI, E. M. K. and TROWELL, H. C.: Neurological disease among African natives of Uganda: review of 269 cases, East African Medical Journal, 1944, XXI, 2.

144. GELFAND, M.: The Sick African, p. 304, The Stewart Printing Co., Capetown, 1944.

145. HEALY, J. W.: Diabetes insipidus as a manifestation of general miliary tuberculosis, Brit. Jour. Child. Dis., 1935, XXXII, 275.

146. HAGENBACH, E.: Ein Fall von Diabetes insipidus, Jahrb. f. Kinderh., 1882, XIX, 214.

147. HAUSHALTER, P. and LUCIEN: Polyurie simple et tubercle de l'hypophyse, Rev. neurol. 1908, XII, 1.

148. HAND, A.: Polyuria and tuberculosis, Arch. Pediat., 1893, X, 673. Defects of membranous bones, exophthalmos and polyuria in childhood: is it dyspituitarism? Am. Jour. Med. Sci., 1921, CLXII, 509.

149. SCHÜLLER, A.: Ueber eigenartige Schädeldefekte im Jungendalter, Fortschr. a. d. Geb. d. Röntgenstrahlen, 1915-16, XXIII, 12.
150. CHRISTIAN, H. A.: Defects in membranous bones, exophthalmos and diabetes insipidus, an unusual syndrome of dyspituitarism, Med. Clin. N. Am., 1919, III, 849. Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, contributions to medical and biological research, vol. 1, p. 390, Paul B. Hoeber, New York, 1919.
151. HOCHSTETTER, F.: Beitrag zur Klinik der Multiplen Blutdrusensklerose, Med. Klin., 1922, XVIII, 661.
152. GRIFFITH, J. P. C.: Xanthoma tuberosum with early jaundice and diabetes insipidus, Arch. Pediat., 1922, XXXIX, 297.
153. ATKINSON, F. R. B.: Schüller-Christian's disease, Brit. Jour. Child. Dis., 1937, XXXIV, 28.
154. SCHULTZ, A., WERMBTER, F. and PUHL, H.: Eigentümliche granulomartige Systemerkrankung des hämatopoetischen Apparates, Virchow's Arch. f. path. Anat., 1924, CCLII, 519.
155. ROWLAND, R. S.: Christian's syndrome and lipoid cell hyperplasias of the reticulo-endothelial system, Ann. Int. Med., 1929, II, 1277. Pediatric investigation of essential xanthomatosis, Schüller-Christian type, Trans. Am. Pediat. Soc., 1932, XLIV, 73.
156. THANNHAUSER, S. J.: Serum lipoids and their value in diagnosis, New England Jour. Med., 1947, CCXXXVII, 546. Lipoidoses, chapter VII-A, Vol. IV, Oxford Medicine, Oxford University Press, 1949.
157. PINKUS, F. and PICK L.: Zur Struktur und Genese der symptomatischen Zanthome, Deutsch. med. Wochnschr., 1908, XXXIV, 1426. PICK L. and PINKUS, F.: Über droppelbrechende Substanz in Hauttumoren ein Beitrag zur Kenntnis des Zanthome, Monatsch. f. prakt. Dermat., 1908, V, 545.
158. CHESTER, W.: Über Lipoidgranulomatose, Virchow's Arch. f. path. Anat., 1930, CCLXXIX, 561. FRASER, J.: Skeletal lipoid granulomatosis (Hand-Schüller-Christian's disease), Brit. Jour. Surg., 1935, XXII, 800. MORISON, J. M. W.: Schüller's disease (reticulo-endotheliosis), Brit. Jour. Radiol., 1934, VII, 213.
159. SOSMAN, M. C.: Zanthomatosis: Schüller-Christian's disease; lipoid histiocytosis, Jour. Am. Med. Assoc., 1932, XCVIII, 110.
160. BLOTNER, H.: Blood fat tolerance tests in malnutrition and obesity, Arch. Int. Med., 1935, LV, 121.
161. THOMA, K. H.: Eosinophilic granuloma with report of one case involving first the mandible, later other bones and being accompanied by diabetes insipidus, Am. Jour. Orthodontics (Oral Surgery Section), 1943, XXIX, 641. JOHNSON, C. I. and ZONDERMAN, B.: Eosinophilic granuloma, report of a case involving the frontal

bone, Ann. Otol., Rhinol., and Laryngol., 1946, LV, 938. GREEN, W. T. and FARBER, S.: Eosinophilic or solitary granuloma (relationship to Hand-Schüller-Christian's disease), Jour. Bone and Joint Surg., 1942, XXIV, 499. MALLORY, T. B.: Medical progress–pathology: diseases of the bone, New Eng. Jour. Med., 1942, CCXXVII, 955. JAFFE, H. L. and LICHTENSTEIN, L.: Eosinophilic granuloma of bone, Arch. Path., 1944, XXVII, 99.
162. MADDOX, K.: Renal dwarfism, Med. Jour. Australia, 1932, I, 487. MITCHELL, A. G.: Nephrosclerosis (chronic interstitial nephritis) in childhood with special reference to renal rickets, Am. Jour. Dis. Child., 1930, XL, 101-145, 345-388.
163. CHARNOCK, D. A.: Renal rickets, Jour. Urol., 1940, XLIV, 850.
164. GITTLEMAN, I. F. and PINCUS, J. B.: Rickets associated with dwarfism, glycosuria, ketonuria and albuminuria, Am. Jour. Dis. Child., 1940, LX, 1351.
165. BIEBER, A.: Diabetes insipidus with pituitary dwarfism and grave renal calculosis: case, Rev. Clin. Pediat., 1946, XLIV, 27.
166. BADER, G. B.: Renal rickets, Jour. Pediat., 1934, IV, 368.
167. MOEHLIG, R. C.: Renal dwarfism or renal rickets, Am. Jour. Roentgenol., 1943, L, 582.
168. LEYDEN: Ein Fall von Diabetes insipidus, Berlin, klin. Wochnschr., 1865, II, 373. OLLIVIER, A.: De la polyurie et des variations de la quantité de l'urée a la suite de l'hémorrhagie cérébrale, Arch. de Physiologie normale et Pathologique, Series 2, 1876, III, 85.
169. LOWENBERG, S. A. and SLOANE, N. G.: Diabetes of 20 years standing improved following subarachnoid hemorrhage, Endocrinology, 1940, XXVII, 191.
170. RASSULEV, J. A.: Ueber Diabetes insipidus bei Pellagra, Arch. f. Schiffs-u. Tropen-Hyg., 1932, XXXVI, 481.
170a. SPIES, T. D.: Personal communication.
171. BELKOWSKI, J.: Actinomycose de la base du crâne et des méniniges; diabète insipide, Rev. de méd., Paris, 1911, XXXI, 415.
172. STRAUCH, A.: Hypophysial dystrophy in hydrocephalus, Jour. Am. Med. Assoc., 1919, LXXII, 1731.
173. LENK, R.: Akute Leukämie und Diabetes insipidus bei Status thymicohypoplasticus, Wien. klin. Wochnschr., 1911, XXIV, 1130.
174. GRÜNTHAL, E. and KELLER, F.: Diabetes insipidus mit Ausfall des hypothalamisch-hypophysären Systems, Monatschr. f. Psychiat. u. Neurol., 1943, CVIII, 254.
175. SHELDON, J. H.: Diabetes insipidus occurring in a case of lymphatic leukemia of the aleukaemic type, Lancet, 1927, I, 489.
176. KUGELMEIER, L. M.: Plotzliches Auftreten eines Diabetes insipidus infolge septischer Nekrose in Hinterlappen und Stiel der Hypophyse

bei akuter myeloischer Stammzellenleukämie, Zeitsch. f. klin. Med., 1937, CXXXII, 521.

177. LESNÉ, E., LAUNAY, C. and SÉE, G.: Diabète insipide au cours l'une maladie de Besnier-Boeck, Bull. et Mém. Soc. méd. d. Hôp. de Paris, 1935, LI, 1137.

178. TILLGREN, J.: Diabetes insipidus as symptom of Schauman's disease, benign lymphogranulomatosis, Brit. Jour. Dermat., 1935, XLVII, 223.

179. TENETA, S. S.: Complications of brucellosis, Klin. Med., 1938, XVI, 120.

180. S. VAISMAN B., S. RAPAPORT T., P. SCHULLER H. and H. MONTES V.: Enfermedad reumatica y diabetes insipida, Rev. méd. de Chile, 1944, LXXII, 419.

181. GURVICH, M. I. and FARIGON, N. E.: Diabetes of malarial origin treated with quinine, case, Sovet. med., 1940, IV, 31.

182. FLINKER, R.: Ein Fall von Dystrophia musculorum progressiva mit Polyurie und Polydipsie, Deutsch. Zeitschr. f. Nervenheilk., 1934, CXXXV, 71.

183. FUTCHER, T. B.: Diabetes insipidus with a report of five cases, Johns Hopkins Hospital Reports, 1902, X, 197.

184. SOPHIAN, A.: Diabetes insipidus and osteitis fibrosa polycystica, Jour. Am. Med. Assoc., 1930, VC, 483.

185. HEARD, J. D., SCHUMACHER, F. L. and GORDON, W. B.: Association of diabetes insipidus with osteitis fibrosa polycystica, Am. Jour. Med. Sci., 1926, CLXXI, 38.

186. BACH, M. J. and MIDDLETON, W. S.: Multiple myeloma and diabetes insipidus, Jour. Am. Med. Assoc., 1931, XCVII, 306.

187. MARIE, J.: Le diabète insipide consideré comme un trouble de le perméabilite des membranes cellulaires du néphron. Hypoperméabilite a l'eau et perméabilite conservée pour sodium chloride, Bull. et Mém. Soc. méd. d. Hôp. de Paris, 1942, LVIII, 239.

188. BLOTNER, H.: The inheritance of diabetes insipidus, Am. Jour. Med. Sci., 1942, CCIV, 261.

189. WEIL, ADOLPH: Über die hereditäre Form des Diabetes insipidus, Virchow's Arch. f. path. Anat., 1884, LXLV, 70.

190. WEIL, ALFRED: Uber die hereditare Form des Diabetes insipidus, Deutsch. Arch. f. klin. Med., 1908, LXLIII, 180.

191. LACOMBE, L. V.: De la polydipsia, Thèse de Paris, No. 99, 1841.

192. TROUSSEAU, A.: Polydipsie, clinique médicale de l'Hotel-Dieu de Paris, 1862, II, 607.

193. LANCERAUX, E.: De la polyurie (diabète insipide), Thèse de Paris, 1869. WACHSMUTH: Ein Fall von Diabetes insipidus, Virchow's Arch. f. path. Anat., 1863, XXVI, 318.

194. CLAY, R. H.: Three cases of diabetes insipidus in one family, Lancet, 1889, I, 1188.
195. EHRMANN: Familiärer Diabetes insipidus bei 5 geistig zuruck gebliebenen Kindern, Berl. klin. Wochnschr., 1911, XLVIII, 496.
196. DEEBREY: Observation de polyurie, Gaz. d. Hôp., 1859, 546.
197. REITH, A.: Polydipsia, treatment by large doses of valerian: improvement, Med. Times and Gaz., 1866, I, 309.
198. ORSI, F.: Curiosità cliniche, sei individui d'una stessa famiglia colpiti da 'idruria, Gazz. Med. Ital., 1881, XLI, 352.
199. MARINESCO, G.: Deux cas de polyurie familiale dite essentielle, Compt. rend. Soc. de Biol., S. 10, 1895, II, 41.
200. MARAÑON, G. and BONILLA, E.: A case of precocious and hereditary diabetes insipidus, Endocrinology, 1925, IX, 467.
201. LANGE, C. DE: Über erblichen Diabetes insipidus, Jahrb. f. Kinderheilk. (3 F.), 1935, LXLV, 1.
202. PAIN, G.: Notes à propos quelques observations de polyurie chronique, p. 19, Thèse de Paris, No. 427, 1879.
203. SASSE, C.: *Ein neuer Fall von hereditärem Diabetes insipidus*, Inaug. Diss., Bonn, 1893.
204. GEE, S.: A contribution to the history of polydipsia, St. Barth. Hosp. Rep., 1877, XIII, 79.
205. LAURITZEN, M.: On hereditaer diabetes insipidus, Hospitalstid, 1893, (Ser. 4), I, 353, 392, 423, 451.
206. KNOPFELMACHER: Diabetes insipidus bei Kindern, Munch. med. Wochnschr., 1905, I, 629.
207. McILRAITH, C. H.: Notes on some cases of diabetes insipidus with marked family and hereditary tendencies, Lancet, 1892, II, 767.
208. CHASE, L. A.: Hereditary diabetes insipidus, Canad. Med. Assoc. Jour., 1927, XVII, 212.
209. CHESTER, W. and SPEIGEL, L.: Hereditary diabetes insipidus, Jour. Am. Med. Assoc., 1933, C, 806.
210. GÄNSSLEN and FRITZ: Über Diabetes insipidus, Klin. Wochnschr., 1924, III, 22.
211. LEVIT, S. G. and PESSIKOVA, L. N.: The genetics of diabetes insipidus and its bearing on the problem of dominance in man, Jour. Hered., 1936, XXVII, 445.
212. ELLERMAN, M.: Hereditary diabetes insipidus, Acta. Psychiat. et Neurol., 1939, XIV, 233.
213. BULLOCH, W.: The treasury of human inheritance, Parts I and II, Section 1a, Diabetes insipidus, Cambridge University Press, Fetter Lane, E. C., University of London, 1909.
214. JUST, G.: Ein Wort zu Weils Diabetes insipidus Stammbaum, Arch. f. Rassen-u. gesellsch.-Biol., 1924-25, XVI, 312.

215. HOGBEN, L.: Genetic Principles in Medicine and Social Science, p. 44, Alfred A. Knopf, New York, 1932.
216. ROGER, H. and ALLIEZ, J.: Diabete insipide familial; à propos de 2 observations personalles, Fol. Neuropath. Eston., 1936, XV-XVI, 37.
217. MARTINEZ and NAVARRON: Zwei Falle der familiaren Form des idiopatischen Diabetes insipidus mit Hypophysenbehandlung, Rev. d. Circ. med. de Cobra, 1922, X, 78.
218. BONNET, R.: Contribution à l'etude du diabète insipide (publication d'un cas de polyurie familial), Lyon, 1936.
219. FRANCESCHETTI, A.: Heterochromia, Bernard-Horner syndrome, dysraphia and familial diabetes with review of case, Rev. d'Oto-neuro-ophth., 1937, XV, 42.
220. KLAFTEN, E.: Diabetes insipidus und Schwangerschaft, Monatschr. f. Geburtsh. u. Gynäk, 1926-27, LXXXV, 333.
221. FORSSMAN, H.: On hereditary diabetes insipidus, Acta Medica Scandanavica, 1945, Supplement 150, p. 1 to 196.
222. HARDING, F. E.: The pituitary antidiuretic hormone in diabetes insipidus—8 cases of diabetes insipidus, 4 with pregnancy, West. Jour. Surg., Obst. and Gyn., 1943, LI, 269.
223. BLOTNER, H.: Diabetes insipidus in one of twins, New Eng. Jour. Med., 1941, CCXXV, 946.
224. ROWNTREE, L. G.: Studies in diabetes insipidus, Jour. Am. Med. Assoc., 1924, LXXXIII, 399.
225. RABINOWITCH, I. M.: Metabolic studies on a case of diabetes insipidus, Arch. Int. Med., 1921, XXVIII, 355.
226. EICHORST, H.: Practische Erfahrungen über die zuckerige und einfache Harnruhr, Cor-bl. f. schweiz. Aerzte, 1888, XVIII, 393.
227. GERHARDT D.: Der Diabetes insipidus, Nothnagel's Specielle Pathologie und Therapie, 1900, VII, 7.
228. FUTCHER, T. B.: A clinical report of nine cases of diabetes insipidus, Trans. Assoc. Am. Phys., 1904, XIX, 247.
229. COHEN, M. MICHAEL and BLOTNER, H.: Unpublished data.
230. CHEYNE, V. D.: A description of the salivary glands of the rat and a procedure for their extirpation, Jour. Dent. Research, 1939, XVIII, 457. TRIMBLE, H. C., ETHERINGTON, J. and LOSCHE, P. K.: Rate of secretion of saliva and incidence of dental caries, Jour. Dent. Research, 1938, XVII, 299. WEISBERGER, D., NELSON, C. T. and BOYLE, P. E.: The development of caries in the teeth of albino rats following extirpation of the salivary glands,

Am. Jour. Orthodontics, 1940, XXVI, 88.

231. STARLING: Principles of Human Physiology, p. 874, edited and revised by C. Lovatt Evans, 8th Edition, Lea and Febiger, Philadelphia, 1941.
232. WEIR, J. F., LARSON, E. E. and ROWNTREE, L. G.: Studies in diabetes insipidus, water balance and water intoxication, study 1, Arch. Int. Med., 1922, XXIX, 306.
233. BLOTNER, H.: Gastric analyses and gastric symptoms in diabetes insipidus, Am. Jour. Digest. Dis., 1940, VII, 73.
234. BLOTNER, H.: Effect of alcohol on digestion by gastric juice, trypsin and pancreatin, Jour. Am. Med. Assoc., 1936, CVI, 1970.
235. DODDS, E. C., NOBLE, R. L., SCARF, R. W. and WILLIAMS, P. C.: Pituitary control of alimentary blood flow and secretions. Changes produced in stomach by the administration of posterior pituitary extract, Proceed. Roy. Soc., London, 1937, CXXIII, 22. CUTTING, W. C., DODDS, E. C., NOBLE, R. L. and WILLIAMS, P. C.: The effect of posterior pituitary extract on the alimentary secretions of intact animals, Ibid., 1937, CXXIII, 27. Pituitary control of alimentary blood flow and secretion. Gastric secretion and blood flow in hypophysectomized animals, Ibid., 1937, CXXIII, 49.
236. DE ANCIAES, C. J. H.: Insuline, pituitrine et secretion gastrique, Compt. rend. Soc. de Biol., 1926, LXLV, 313.
237. KAULBERSZ, J., PATTERSON, T. L., SANDWEISS, D. J. and SALTZSTEIN, H. C.: Alterations in urogastrone excretion produced by extirpation of various endocrine glands, Am. Jour. Physiol., 1947, CL, 373.
238. MARAÑON, G., RICHET, C., PERGOLA, A. and LESUEUR, G.: Acute abdominal syndromes of hypophyseal origin, Lisboa Médica, Lisbon, 1939, XVI, 589, abstract, Jour. Am. Med. Assoc., 1940, CXIV, 198.
239. SNELL, A. M.: Water intoxication in diabetes insipidus, Med. Clin. North America, 1928-29, XII, 1667.
240. ICHIJO, T.: The effects of extract of pituitary gland on the sedimentation of red blood corpuscles of the normal and hypophysectomized dogs, Sei-I-Kwai Med. Jour., 1934, LIII, June abstract Sect., p. 5.
240a. KOURILSKY, R. and FOURNIER, E.: Étude physiopathologique du diabète insipide humain, Ann. de Méd., 1948, IL, 135.
241. KEITH, N. M., ROWNTREE, L. G. and GERAGHTY, J. T.: A method for the determination of plasma and blood volume, Arch. Int. Med., 1915, XVI, 547.

242. GIBSON, J. G., Jr. and EVANS, W. A., Jr.: Clinical studies of the blood volume. 1. Clinical application of a method employing the azo dye "Evans blue" and spectrophotometer, Jour. Clin. Invest., 1937, XVI, 301.
243. FISCHER, W. J. H., Jr. and BECK, I.: Personal communication.
244. TALBOTT, T. H., COOMBS, F. S., CANSOLAZIO, W. V. and PECORA, L. J.: Diabetes insipidus associated with diabetes mellitus, metabolic studies and report of a case, Arch. Int. Med., 1940, LXVI, 607.
245. SOULE, S. D.: Diabetes insipidus and pregnancy, Am. Jour. Obst. and Gyn., 1937, XXXIII, 878.
245a. CHIN, H. I., LIU, S. H. and YU, T. F.: Water and electrolyte metabolism in diabetes insipidus, Proceed. Soc. Exper. Biol. and Med., 1941, XLVI, 682.
246. FISCHER, W. J. H., Jr. and BOWMAN, R. O.: The effect of intravenous solutions on the plasma volume, hematocrit, plasma protein and urinary output in the convalescent patient, read before regional meeting of the American College of Physicians, Hanover, New Hampshire, January 28, 1947, unpublished to date.
247. FOLIN, O. and WU, H.: A system of blood analysis, supplement 1, a simplified and improved method for determination of sugar, Jour. Biol. and Chem., 1920, XLI, 367.
248. MOSENTHAL, H. O.: Interpretation of sugar tolerance tests, Med. Clin. North America, p. 299, (March) 1947.
249. BLOTNER, H.: Sugar tolerance tests, methods and evaluation, Am. Jour. Digest. Dis., 1947, XIV, 245. Diagnosis of diabetes mellitus, Proceed. Am. Diabetes Assoc., 1947, VII, 153.
250. GIBSON, R. B., MAGERS, E. J. and DULANEY, H.: Blood sugar curves in diabetes insipidus and in habitual and experimental excessive water drinking, Endocrinology, 1927, XI, 341.
251. JOHN, H. J.: Glucose tolerances and its value in diagnosis, Jour. Metab. Res., 1922, L, 497; 1923, IV, 255.
252. LAWRENCE, R. D. and HEWLETT, R. F. L.: The effect of pituitrin and insulin on blood sugar, Brit. Med. Jour., 1925, I, 998.
253. BLOTNER, H. and FITZ, R.: The effect of insulin, pituitrin and adrenalin on the blood sugar level, Jour. Clin. Invest., 1927, V, 51.
254. BLOTNER, H.: Blood fat tolerance tests in malnutrition and obesity, Arch. Int. Med., 1935, LV, 121.
255. JOSLIN, E. P.: Fat and the diabetic, New England Jour. Med., 1933, CCIX, 519.
256. BLOOR, W. R.: The determination of small amounts of lipid in blood plasma, Jour. Biol. Chem., 1928, LXXVII, 53.

257. RONY, H. R. and LEVY, A. J.: *Fat tolerance in obesity, Jour. Lab.* and Clin. Med., 1929, XV, 221.
258. CHAIKOFF, I. L., McGAVACK, T. H. and KAPLAN, A.: The blood lipids in the post absorptive state and after the ingestion of fat in normal human subjects and in a case of disseminated cutaneous xanthomata, Jour. Clin. Invest., 1934, XIII, 1.
259. ANSELMINO, K. J. and HOFFMAN, F.: *Das* Fettstoffwechselhormon der Hypophysenvorderlappens, Klin. Wochnschr., 1931, X, 2380.
260. GOLZIEHER, M. A., SHERMAN, I. and ALPERSTEIN, B. B.: The fat tolerance test in pituitary disease, Endocrinology, 1934, XVIII, 505.
261. *MUNOZ, J. M.: Action de l'extract antéro-hypophysaire sur les lipids* du sang, Compt. rend. Soc. de Biol., 1933, CXII, 502.
262. EVANS, E. I.: Diabetogenic principle of the anterior pituitary, Proceed. Soc. Exper. Biol. and Med., 1933, XXX, 1370.
263. COOPE, R. and CHAMBERLAIN, E. N.: The effect of pituitrin on the fatty acid of the liver, Jour. Physiol., 1925, LX, 69.
264. *NEUBAUER, C. and VOGEL, J.: Anleitung zur qualitativen und* quantitativen Analyse des Harns, p. 353, Kreidel, Wiesbaden, 1872.
265. OPPENHEIM, H.: Casuisticher Beitrag zur Polyurie, Zeitschr. f. klin. Med., 1882, V, 618. Weiterer Beitrag zur Polyurie, Zeitschr. f. klin. Med., 1883, VI, 556.
266. FITZ, R.: A case of diabetes insipidus, Arch. Int. Med., 1914, XIV, 706.
267. ROSENBLOOM, J. and PRICE, H. T.: A metabolism study of a case of diabetes insipidus, Am. Jour. Dis. Child., 1916, XII, 53.
268. CURTIS, G. M.: The production of experimental diabetes insipidus, Arch. Int. Med., 1924, XXXIV, 801.
269. SWAN, H. G.: Sodium chloride and diabetes insipidus, Am. Jour. *Physiol., 1939, CXXVI,* 341.
270. PETERS, J. P.: Body Water, p. 323, Charles C. Thomas, Springfield, Illinois, 1935.
271. VEIL, W. H.: Über intermediäre Vorgänge beim Diabetes insipidus und ihre Bedeutung für die Kenntnis von Wesen dieses Leidens, Biochem. Zeitschr., 1918, XCI, 317.
272. *BUTLER, A. M., HARPER, E. A.* and CAREY, B. W., Jr.: Excretion of sodium and chloride in normal persons and in patients with nephritis and diabetes insipidus, Am. Jour. Dis. Child., 1933, XLVI, 1459.
273. WILLIAMS, J. R.: Diabetes insipidus. A metabolic study of the effect of pituitary administration, Endocrinology, 1917, I, 312.

242. GIBSON, J. G., Jr. and EVANS, W. A., Jr.: Clinical studies of the blood volume. 1. Clinical application of a method employing the azo dye "Evans blue" and spectrophotometer, Jour. Clin. Invest., 1937, XVI, 301.
243. FISCHER, W. J. H., Jr. and BECK, I.: Personal communication.
244. TALBOTT, T. H., COOMBS, F. S., CANSOLAZIO, W. V. and PECORA, L. J.: Diabetes insipidus associated with diabetes mellitus, metabolic studies and report of a case, Arch. Int. Med., 1940, LXVI, 607.
245. SOULE, S. D.: Diabetes insipidus and pregnancy, Am. Jour. Obst. and Gyn., 1937, XXXIII, 878.
245a. CHIN, H. I., LIU, S. H. and YU, T. F.: Water and electrolyte metabolism in diabetes insipidus, Proceed. Soc. Exper. Biol. and Med., 1941, XLVI, 682.
246. FISCHER, W. J. H., Jr. and BOWMAN, R. O.: The effect of intravenous solutions on the plasma volume, hematocrit, plasma protein and urinary output in the convalescent patient, read before regional meeting of the American College of Physicians, Hanover, New Hampshire, January 28, 1947, unpublished to date.
247. FOLIN, O. and WU, H.: A system of blood analysis, supplement 1, a simplified and improved method for determination of sugar, Jour. Biol. and Chem., 1920, XLI, 367.
248. MOSENTHAL, H. O.: Interpretation of sugar tolerance tests, Med. Clin. North America, p. 299, (March) 1947.
249. BLOTNER, H.: Sugar tolerance tests, methods and evaluation, Am. Jour. Digest. Dis., 1947, XIV, 245. Diagnosis of diabetes mellitus, Proceed. Am. Diabetes Assoc., 1947, VII, 153.
250. GIBSON, R. B., MAGERS, E. J. and DULANEY, H.: Blood sugar curves in diabetes insipidus and in habitual and experimental excessive water drinking, Endocrinology, 1927, XI, 341.
251. JOHN, H. J.: Glucose tolerances and its value in diagnosis, Jour. Metab. Res., 1922, L, 497; 1923, IV, 255.
252. LAWRENCE, R. D. and HEWLETT, R. F. L.: The effect of pituitrin and insulin on blood sugar, Brit. Med. Jour., 1925, I, 998.
253. BLOTNER, H. and FITZ, R.: The effect of insulin, pituitrin and adrenalin on the blood sugar level, Jour. Clin. Invest., 1927, V, 51.
254. BLOTNER, H.: Blood fat tolerance tests in malnutrition and obesity, Arch. Int. Med., 1935, LV, 121.
255. JOSLIN, E. P.: Fat and the diabetic, New England Jour. Med., 1933, CCIX, 519.
256. BLOOR, W. R.: The determination of small amounts of lipid in blood plasma, Jour. Biol. Chem., 1928, LXXVII, 53.

290. MAURER, F. E.: Ueber den Jodgehalt des Blutes und seine Veränderungen in Menstruation und Graviditat, Arch. f. Gynak., 1927, CXXX, 70.

291. NITZECU, I. I. and BINDER, E.: Iodemio normale: variations saisonniers: iodemie des goitreux, Compt. rend. Soc. de Biol., 1931, CVIII, 279.

292. *DAVIS, C. B., CURTIS, G. M. and COLE, V. V.: Blood iodine* studies: II The normal iodine content of human blood, Jour. Lab. & Clin. Med., 1934, XIX, 818.

293. McCULLAGH, D. R.: Studies in blood iodine by the use of a new chemical method, Cleveland Clinic Quarterly, 1935, II, 15.

294. PERKIN, H. J. and CATTELL, R. B.: The practicability and significance of blood iodine estimations, New York State Jour. Med., 1936, XXXVI, 1033.

295. UNPUBLISHED DATA.

296. CURTIS, G. M. and PUPPEL, I. D.: Increased urinary excretion of iodine in hyperthyroidism, Arch. Int. Med., 1937, LX, 498.

297. PERKIN, H. J. and HURXTHAL, L. M.: The fractionation of the iodine of the blood in thyroid disease, Jour. Clin. Invest., 1939, XVIII, 733.

298. *PERKIN, H. J., BROWN, B. B. and LANG, J.: Blood iodine con*tent of normal and thyrotoxic individuals; iodine tolerance test, Canad. Med. Assoc. Jour., 1934, XXXI, 365. PERKIN, H. J. and LAHEY, F. H.: The iodine tolerance test as an aid in the diagnosis of clinical hyperthyroidism, New Eng. Jour. Med., 1937, CCXVI, 501.

299. FITZ, R. and HUNT, R. S.: Experiences with an iodine tolerance test in hypothyroid patients, Trans. Assoc. Am. Physicians, 1937, LII, 24.

300. WINER, N. J. and BLOTNER, H.: Renal function in diabetes insipidus, Arch. Int. Med., 1942, LXX, 61.

301. BLOTNER, H.: Alcohol tolerance tests in normal individuals and in patients with diabetes mellitus and diabetes insipidus, New Eng. Jour. Med., 1939, CCXX, 283.

302. GIBSON, J. G., 2ND, and BLOTNER, H.: The determination of ethyl alcohol in blood and urine with the photoelectric colorimeter, Jour. Biol. Chem., 1938, CXXVI, 551.

303. AMBARD, L.: Physiologie Normale et Pathologique des Reins, p. 15, Second edition, Masson & Cie, Paris, 1920.

304. WIDMARK, E. M. P.: Über die Konzentration des genossenen Alkohols in Blut und Harn unter verschiedenen Umstanden, Skandinav. Arch. f. Physiol., 1916, XXXIII, 85.

305. HAGGARD, H. W. and GREENBERG, L. A.: Studies in absorption, distribution and elimination of ethyl alcohol; the excretion

274. BLUMGART, H. L.: Diabetes insipidus with particular reference to further experience with treatment by pituitary extract applied intranasally, Med. Clin. North America, 1932, XV, 895.
275. WEIR, J. F.: Pituitary extract on metabolism of diabetes insipidus, Arch. Int. Med., 1923, XXXII, 617.
276. WHITE, H. L. and FINDLEY, T., JR.: Responses of normal subjects and of patients with diabetes insipidus to water and salt ingestion, Jour. Clin. Invest., 1939, XVIII, 377.
277. WINTER, C. A., INGRAM, W. R. and GROSS, E. G.: Effect of pitressin injections upon the serum electrolytes and water exchange of cats with diabetes insipidus and adrenal insufficiency, Am. Jour. Physiol., 1939, CXXVI, 656.
278. SMITH, F. M. and MACKAY, E. M.: Influence of posterior pituitary extract on sodium balance in normal subjects and in patients with diabetes insipidus, Proceed. Soc. Exp. Biol. and Med., 1936, XXXIV, 116.
279. MAINZER, F.: Uber Fragen der Hypophysenhinterlappentherapie des Diabetes insipidus, Wien. Arch. Inn. Med., 1935, XXVI, 101.
280. BLOTNER, H.: Blood and urine chlorides in 22 cases with diabetes insipidus, Am. Jour. Med. Sci., 1941, CCII, 222.
281. BLOTNER, H.: The calcium and phosphorus in the cerebrospinal fluid in diabetes insipidus, Am. Jour. Med. Sci., 1940, CC, 239.
282. MANCHESTER, R. C.: Influence of posterior pituitary extracts on mineral and water exchange in children, Proceed. Soc. Biol. and Med., 1931-32, XXIX, 717.
283. FULTON, M. N., VAN AUKEN, H. A., PARSONS, R. J. and DAVENPORT, L. F.: Comparative effect of various diuretics in dogs with special reference to excretion of urine, chloride and urea, Jour. Pharm. and Exp. Ther., 1934, L, 223.
284. LINDEBOOM, G. A.: Beobachtungen bei einem Fall von Diabetes insipidus et mellitus, Deutsch. Arch. f. klin. Med., 1933, LXXIV, 175.
285. BLOTNER, H.: The amount of iodine in the blood and urine in patients with diabetes insipidus, Am. Jour. of Med. Sci., 1942, CCIII, 708.
286. PERKIN, H. J. and LAHEY, F. H.: The level of iodine in the blood, Arch. Int. Med., 1940, LXV, 882.
287. PERKIN, H. J.: Determination of iodine in the blood, Biochem. Jour., 1933, XXVII, 1078.
288. CURTIS, G. M. and PUPPEL, I. D.: The normal urinary iodine in man, J. Lab. and Clin. Med., 1937, XXII, 1014.
289. SCHERINGER, W.: Beitrag zur Kenntnis des Blutjodspiegels beim Weibe unter physiologischen Bedingungen, Arch. f. Gynäk., 1930, CXLIII, 319.

321. BLOTNER, H. and KUNKEL, P.: Diabetes insipidus and pregnancy, New England Jour. Med., 1942, CCXXVII, 287.
322. FRENCH, H.: The influence of pregnancy upon certain medical diseases, and of certain medical diseases upon pregnancy, Brit. Med. Jour., 1908, I, 1165-1172.
323. BOISSARD: Discussion of Chavane and Faure-Miller (337).
324. BAR: Discussion of Chavane and Faure-Miller (337).
325. KOLLE: Demonstration: Gravidtät bei Diabetes insipidus, Zentralbl. f. Gynäk., 1926, L, 2212.
326. ARTAUD, A.: Un cas de grossese au cours d'un diabète insipide, Bull. Soc. d'Obst. et de Gynéc., 1933, XXII, 196-198.
327. SOULE, S. D.: Diabetes insipidus and pregnancy, Am. Jour. Obst. and Gynec., 1937, XXXIII, 878-890.
328. VERDEUIL and CASALTA: Une observation de diabète insipide et gravidité, Bull. Soc. d'Obst. et de Gynéc., 1938, XXVII, 87.
329. MOMIGLIANO, E.: Diabete insipido e gravidanza, Ann. di Ostet. e Ginec., 1929, LI, 905-979.
330. DUNCAN, J. M.: On diabetes insipidus in pregnancy and labour, Trans. Obst. Soc., London, 1888, XXIX, 308-316.
331. VINAY, C.: Diabète insipide et grossesse, Semaine méd., 1899, XIX, 14.
332. MERBACH: Cited by Müller, P.: Die Krankheiten des weiblichen Körpers in ihren Wechselbeziehungen zu den Geschlechtsfunctionen, p. 508, Stuttgart, 1888.
333. KATZ, H.: Cited by HEIDLER, H. (348), Zentralbl. f. Gynäk., 1924, XLVIII, 357-363.
334. DUVOIR, M., POLLET, L. and CACHIN, M.: Diabète insipide suivi de diabète sucré avec coma: influence de grossesses sur la polyurie: traitment par la folliculine, Bull. et Mém. Soc. méd. d. Hôp. de Paris, 1932, XLVIII, 549-551.
335. CARTER, P. J.: Diabetes insipidus in pregnancy: case report, Urol. and Cutan. Rev., 1940, XLIV, 549-551.
336. THOMSON, K. J., HIRSHEIMER, A., GIBSON, J. G., Jr. and EVANS, W. A., Jr.: Studies on circulation in pregnancy. III. Blood volume changes in normal pregnant women, Am. Jour. Obst. and Gyn., 1938, XXXVI, 48-59.
337. CHAVANE and FAURE-MILLER, R.: Diabète insipide et grossesse, Bull. Soc. d'Obst. et de Gynéc., 1900, III, 400-409.
338. KLAFTEN, E.: Diabetes insipidus and Schwangerschaft, Monatschr. f. Geburtsh. u. Gynak, 1927, LXXV, 333-349.
339. BALLERINI: Per la genesi del diabete insipido e delle poliurie gravidiche, Folia Gynaec, 1921, XIV, 97.

of alcohol in urine and expired air; the distribution of alcohol between air and water, blood and urine, Jour. Pharmacol. and Exper. Therap., 1934, LII, 150.
306. NEWMARK, L.: A case of infundibular tumor in a child causing diabetes insipidus with tolerance of alcohol, Arch. Int. Med., 1917, XIX, 550.
307. MILES, W. R.: The comparative concentrations of alcohol in human blood and urine at intervals after ingestion, Jour. Pharmacol. and Exper. Therap., 1922, XX, 265.
308. WIDMARK, E. M. P.: Hormonale Einflüsse auf den Alkoholumsatz, Biochem. Zeitschr., 1935, CCLXXXII, 79.
309. BLOTNER, H.: The calcium and phosphorus in the cerebronspinal fluid in diabetes insipidus, Am. Jour. Med. Sci., 1940, CC, 235.
310. CLARK, E. P. and COLLIP, J. B.: Tisdall method for determination of blood serum calcium with a suggested modification, Jour. Biol. Chem., 1925, LXIII, 461.
311. FISKE, C. H. and SUBBAROW, Y.: Colorimetric determination of phosphorus, Jour. Biol. Chem., 1925, LXVI, 375.
312. MERRITT, H. H. and FREMONT-SMITH, F.: The Cerebrospinal Fluid, p. 27, W. B. Saunders Co., Philadelphia, 1938.
313. McLEAN, F. C. and HASTINGS, A. B.: The state of calcium in the fluids of the body, Jour. Biol. Chem., 1935, CVIII, 285.
314. CANTAROW, A.: The calcium content of cerebrospinal fluid, Arch. Int. Med., 1929, XLIV, 667. The relationship between the calcium content of cerebrospinal fluid and blood serum, Arch. Int. Med., 1929, XLIV, 670.
315. MERRITT, H. H. and BAUER, W.: The calcium content of serum, cerebrospinal fluid and aqueous humor at different levels of parathyroid activity, Jour. Biol. Chem., 1931, XC, 215.
316. COHN, D. J., KAPLAN, I. and LEVINSON, A.: A study of calcium and phosphorus in cerebrospinal fluid, Jour. Lab. and Clin. Med., 1939, XXIV, 609.
317. GREGORY, R. and ANDERSCH, M.: The filterable calcium of blood serum, a comparison of filterable calcium of serum and total calcium of cerebrospinal fluid in normal, hyperparathyroid and hypoparathyroid states, Am. Jour. Med. Sci., 1936, CXCI, 263.
318. McLEAN, F. C. and HASTINGS, A. B.: Clinical estimation and significance of calcium ion concentration in the blood, Am. Jour. Med. Sci., 1935, CLXXXIX, 601.
319. BRYAN, A. H. and METZGER, M. A.: The insensible loss of water in diabetes insipidus, Am. Jour. Med. Sci., 1938, CXCVI, 23.
320. S. A. ROBINS, Professor of Roentgenology at Tufts College Medical School, made the intravenous urograms.

359. NOVAK, J.: Diabetes insipidus in graviditate, Berl. klin. Wochnschr., 1917, LIV, 107-109.
360. VICKERS, D. M.: Diabetes insipidus with acute retention in pregnancy: report of a case, Surg., Gynes. and Obst., 1924, XXXVIII, 223-225.
361. LAURENTIE, A. and BASILIOU, B. J.: Crisis éclamptiques sans albuminurie avant apparu le 22e jour des suites de couches amaurose et diabete insipide contribution a l'étude pathogénique du diabète insipide dans ses rapports avec l'eclampsie, Gynec. et Obst., 1926, XIII, 321-331.
362. JANSEN, R.: Über Diabetes Insipidus (ein Besonderer Fall), Inaugural Dissertation, Halle, C. A. Kaemmerer & Co., 1899.
363. FELLETAAR, J.: Diabetes insipidus and pregnancy, Orvosi hetil., 1929, LXXIII, 701.
364. MARAÑON, G.: Un caso de diabetes insipida gravídica con poliuria enorme y probable lesión tuberculosa de lóbula posterior de hipófisis, Arch. Med. Madr., 1926, XXII, 289.
365. PRIBRSKY, J.: Diabetes insipidus and pregnancy, Časop. lék. cesk., 1934, LXXIII 260, 299 and 322.
366. SCHELLENBERG, P.: Diabetes insipidus und Graviditat: ein Beitrag. zur Aetiologie des Diabetes insipidus, p. 61, Inaugural Dissertation, Königsberg, Johan Raabe, 1930.
367. LAUTER, S. and HILLER, F.: Diabetes mellitus and Diabetes insipidus in Auschluss an Schwangerschaft, Deutsches Arch. f. klin. Med., 1925, CXLVI, 355-361.
368. SKROBSNSKI, K. K.: Über das Verhältnis des Diabetes mellitus und insipidus zu den weiblichen Geschlechtsorgane und Schwangerschafte, Zentralbl. f. Gynäk., 1902, XXVI, 1038.
369. KLEINWACHTER, L.: Der Diabetes von gynäkologischen Standpunkt aus betrachtet. Zeitschr. f. Geburtsh. u. Gynak., 1898, XXXVIII, 191-233.
370. HENRIET, P.: Glycosuries et diabètes en pratique obstétricale, Rev. franç. de Gynéc. et d'Obst., 1936, XXXI, 111-128.
371. SILVA, G.: Diabetes insipidus und Schwangerschaft, Bol. an clin. Obst., Santiago del Chile, 1927, XIV, 77.
372. DELLEPIANE, G.: Sul diabete insipido complicante la gravidanza, Boll. d. Soc. Piemontese di Ostet. de Ginec., 1934, II, 429-450.
373. SPAIN, A. W. and GEOGHEGAN, F.: Diabetes insipidus in association with postpartum pituitary necrosis, Jour. Obstet. and Gynec. Brit. Emp., 1946, LIII, 223.
374. SHEEHAN, H. L. and MURDOCH, R.: Postpartum necrosis of anterior pituitary, pathological and clinical aspects, Jour. Obstet. and Gynecol. Brit. Emp., 1938, XLV, 456.

340. BENNETT, J. H.: Clinical Lectures on the Principles and Practice of Medicine, p. 1037, Fifth Edition, Edinburgh, 1868.
341. DUNCAN, J. M.: On diabetes insipidus in pregnancy and labour, Trans. Obst. Soc., London, 1888, XXIX, 308-316.
342. SHAMBERG, J. F.: A case of exaggerated polyuria of pregnancy, Univ. Mag., 1893-94, VI, 385.
343. VOITURIEZ, J.: De la polyurie gravidique, J. de Soc. méd. de Lilles, 1890, I, 457-467.
344. ESTERLE: Cited by TARNIER, S. and BUDIN, P.: Traité de l'art des Accouchements, vol. II, p. 586, G. Steinheil, Libraire-Éditeur, Paris, 1886.
345. VINAY, C.: Diabète insipide et grossesse, Semaine méd., 1899, XIX, 14.
346. NOVAK, J.: Diabetes insipidus in graviditate, Berl. klin. Wochnschr., 1917, LIV, 107-109.
347. LICHWITZ, L.: Drei Fälle von Simmondscher Krankheit, Klin. Wochnschr., 1922, I, 1877-1879.
348. HEIDLER, H.: Kongenitale Hautdefekte bei Neugeborenen, Zentralbl. f. Gynäk, 1924, XLVIII, 357-363.
349. FRUHINSHOLZ, A., VERMELIN, H. and HENNEQUIN: Diabète d'origine hypophysaire et gestation, Bull. Soc. d'Obst., et Gynéc., 1928, XVII, 741-744.
350. EDELMANN, J. G. and KRITZMAN, A. S.: Ein Fall von Diabetes insipidus bei einer Schwangeren mit Lues ignorata, Bericht ü. d. ges. Gynäk. u Geburtsh., 1926, X, 325.
351. MESTITZ, W.: Ein Fall von transitorischer Polyurie und Polydipsie am normalen Schwangerschaftsende, Zeitschr. f. Geburtsh. u. Gynäk., 1930, LXLVIII, 123-129.
352. ANSELMINO, K. J. and HOFFMAN, F.: Diabetes insipidus und Schwangerschaft, Zentralbl. f. Gynäk., 1930, LIV, 2061-2068.
353. DIETEL, H.: Diabetes insipidus und Schwangerschaft, Arch. f. Gynäk., 1935, CLIX, 404-409.
354. BRATTSTROM, E.: Ein Fall von Diabetes insipidus traumaticus und Gravidität, Acta Obst. et Gynéc. Scandinav., 1938, XVIII, 320-324.
355. BLEAKLY, J.: Case of diabetes insipidus and twin pregnancy, Proceed Roy. Soc. Med., 1938, XXXI, 1062-1064.
356. MERLINO, A.: Diabete insipido complicante la gravidanza, Arch. di Ostet. e. Ginec., 1938, II, 121-143.
357. HART, S. D. and BREITMAN, H. B.: Diabetes insipidus complicating pregnancy, Am. Jour. Obst. and Gynec., 1941, XLI, 527.
358. EDELMANN, J. G. and KRITZMAN, A. S.: Ein Fall von Diabetes insipidus bei einer Schwangeren mit Lues ignorata, Bericht u. d. ges. Gynak. u. Geburtsh., 1926, X, 325.

389. JOSLIN, E. P., ROOT, H. F., WHITE, P., MARBLE, A. and BAILEY, C. C.: The treatment of diabetes mellitus, Lea and Febiger, Philadelphia, 1946, p. 725.
390. STEINER, F.: Zur Erblichkeit des Diabetes insipidus, Der Erbarzt, 1939, VII, 89.
391. HOUSSAY, B. A.: Carbohydrate metabolism, New England Jour. Med., 1936, CCXIV, 971.
392. LONG, C. N. H.: The influence of the pituitary and the adrenal glands upon pancreatic diabetes, Medicine, 1937, XVI, 215.
393. YOUNG, F. G.: Experimental investigations on relationship of anterior hypophysis to diabetes mellitus, Proc. Roy. Soc. Med., 1938, XXXI, 1305.
394. HAM, A. W. and HAIST, R. E.: Histological study of trophic effects of diabetogenic anterior pituitary extracts and their relation to the pathogenesis of diabetes, Am. Jour. Path., 1941, XVII, 787.
395. RICHTER, C. P.: Experimental diabetes insipidus: its relationship to the anterior and posterior lobes of the hypophysis, Am. Jour. Physiol., 1934, CX, 439.
396. MOMPO ALIÑO, L.: Association of diabetes mellitus and diabetes insipidus in hypophyseal infantalism, heterologous transplantation of pituitary body, Rev. Clin. españ., 1941, II, 31.
397. LINDEBOOM, G. A.: Beobachtungen bei einem Fall von Diabetes insipidus et mellitus, Deutsches Arch. Für Klin. Med., 1933, CLXXV, 74.
398. MOLONEY, G. E.: Diabetes mellitus associated with diabetes insipidus, New Zealand Med. Jour., 1939, XXXVIII, 263.
399. RUTLEDGE, D. I., and RYNEARSON, E. H.: Diabetes insipidus. Treatment by insufflation of powdered substances, Proc. Staff Meet., Mayo Clinic, 1939, XIV, 443.
400. SCHÜNTERMANN, C. E.: Fall von Diabetes insipidus mit Diabetes mellitus, Klin. Wochnschr., 1930, IX, 22.
401. HEIBERG, K. A.: Ein Fall von gleichzeitigem Diabetes insipidus und diabetes mellitus, Ztschr. f. Klin. Med., 1911, LXXIII, 319.
402. FREUND, H.: Untersuchungen uber einem Fall von Gleichzeitig bestehenden Diabetes mellitus and insipidus, Klin. Wochnschr., 1922, I, 1780.
403. CIPRIANI, C. R., MORACCHINI, R. and ROLTTA, C.: Diabetes insipido e diabetes mellito in acromegalica con struma adenoma del l'ipofise e sclerosis del pancreas, Arch. per le Sc. med., 1929, LIII, 337.
404. di GUGLIELMO, G.: Diabete mellito e lesioni ipofisarie, Boll. d. Soc. med. chir. di Pavia, 1927, II, 319.

375. TROISIER, J.: Action antipolyuriques des hautes doses de folliculine dans le diabète insipide de l'homme, Bull. et Mém Soc. méd. d. Hôp. de Paris, 1932, XLVIII, 1451.
376. BELTRAMETTI, L.: Die Sexual funktionen in ihren Beziehungen zum Wasserhaushalt insebesondere zum Diabetes insipidus, Endokrinologie, 1935, XVI, 241.
377. BLOTNER, H.: Effect of amniotin and antuitrin-S in diabetes insipidus, New England Jour. Med., 1937, CCXVII, 592.
378. HARDING, F. E.: The pituitary antidiuretic hormone in diabetes insipidus. Eight cases of diabetes insipidus—four with pregnancy, West. Jour. Surg., Obst. and Gyn., 1943, LI, 269.
378a. DANDY, W. E.: Section of the human hypophysial stalk. Its relation to diabetes insipidus and hypophyseal function, Jour. Am. Med. Assoc., 1940, CXIV, 312.
379. FISHER, C., MAGOUN, H. W. and RANSON, S. W.: Dystocia in diabetes insipidus: the relation of pituitary oxytocin to parturition, Am. Jour. Obst. and Gyn., 1938, XXXVI, 1.
380. SENATOR, H.: Ueber die Beziehungen zwischen Diabetes mellitus und insipidus, Deutsches med. Wochnschr., 1897, XXIII, 385.
381. GREENE, J. A. and GIBSON, R. B.: Coexistance of diabetes mellitus and diabetes insipidus, Jour. Lab. and Clin. Med., 1938-39, XXIV, 455.
382. ALLAN, F. N. and ROWNTREE, L. G.: The association of diabetes insipidus and diabetes mellitus, Endocrinology, 1931, XV, 97.
382a. BANERJEE, S.: A case of diabetes insipidus associated with diabetes mellitus, Indian Med. Gaz., 1947, LXXXII, 478.
383. LAWRENCE, R. D. and McCANCE, R. A.: Diabetes mellitus and diabetes insipidus associated in one case, Lancet, 1933, I, 76.
384. McPHERSON, E.: Case of diabetes mellitus associated with lesions of the pituitary body, Glasgow Med. Jour., 1939, CXXXI, 220.
385. TALBOTT, J. H., COOMBS, F. S., CONSOLAZIO, W. V. and PECORA, L. J.: Diabetes insipidus associated with diabetes mellitus, metabolic studies and report of a case, Arch. Int. Med., 1940, LXVI, 607.
386. LEWIN, C.: Zur Frage des Zusammenhangs des Diabetes mellitus und Diabetes insipidus, Med. Klin., 1919, XV, 133.
387. TESCHEMACHER: Ueber die Fortdauer der Polyurie bei Diabetikern nach vollständig verschwundener Glykosurie und der Uebergang von Diabetes mellitus in Diabetes insipidus, München Med. Wochnschr., 1907, I, 561.
388. D'AMATO, L.: Due casi di diabete insipido trasformati in diabete mellito, Riforma med., 1902, II, 411.

pituitary extract and the influence of ephedrine thereupon, Jour. Pharmacol. and Exper. Therap., 1938, LXIV, 86.
419. STARR, I., GAMBLE, C. J., MARGOLIES, A., DONAL, J. S., Jr., JOSEPH, N. and EAGLE, E.: A clinical study of the action of 10 commonly used drugs on cardiac output, work and size, on respiration, on metabolic rate, and on electrocardiograms, Jour. Clin. Invest., 1937, XVI, 799.
420. LOWELL, F. C.: Immunologic studies in insulin resistance. I. Report of a case exhibiting variations in resistance and allergy to insulin, Jour. Clin. Invest., 1944, XXIII, 225. Immunologic studies in insulin resistance. II. The presence of a neutralized factor in the blood exhibiting some characteristics of an antibody, Jour. Clin. Invest., p. 233. Immunologic studies in insulin resistance. III. Measurement of an insulin antagonist in the serum of an insulin-resistant patient by the blood sugar curve method in mice, Jour. Clin. Invest., 1947, XXVI, 57.
420a. WILLIAMS, R. H. and COLE, H.: Nephrogenic diabetes insipidus. transmitted by females and appearing during infancy in males, Ann. Int. Med., 1947, XXVII, 84.
421. GREENE, J. A. and JANUARY, L. E.: Diabetes insipidus treated by the subcutaneous administration of a suspension of pitressin tannate in oil, Jour. Am. Med. Assoc., 1940, CXV, 1183. Efficacy of pellets of posterior hypophysis and of pitressin in oil in diabetes insipidus, Proceed Soc. Exper. Biol. & Med., 1940, XLIV, 217.
422. STEPHENS, D. J.: Pitressin in oil; prolonged antidiuretic effect in experimental and clinical diabetes insipidus, Jour. Clin. Invest., 1941, XX, 463.
423. THORN, G. W. and STEIN, K. E.: Diabetes insipidus and pitressin; pitressin tannate therapy in diabetes insipidus, Jour. Clin. Endocrinology, 1941, I, 680.
424. BLOTNER, H.: Pitressin tannate in oil in the treatment of diabetes insipidus, Jour. Am. Med. Assoc., 1942, CXIX, 995.
425. LACY, C. S.: Three cases of diabetes insipidus successfully treated by ergot, Med. News, 1883, XLII, 9.
426. EICHORST, H.: Praktische Erfahrungen über die zuckerige und einfache Harnruhr, Cor.-Bl. f. Schweiz. Aertze, 1888, XVIII, 393. SCHERF, D.: Pyramidon beim Diabetes insipidus, Wien, Arch. f. inn. Med., 1932, XXII, 457. DeGOWIN, E. L.: Diabetes insipidus, Am. Jour. Med. Sci., 1935, CXC, 747.
427. KAHN, B. S.: Use of amidopyrine in a case of diabetes insipidus, Jour. Am. Med. Assoc., 1933, C, 1593.
428. GRANT, F. C.: Surgical experience with tumors of the pituitary gland, Jour. Am. Med. Assoc., 1948, CXXXVI, 668.

405. GRAY, P. A. and MOFFAT, W. M.: Coexistance of diabetes mellitus and diabetes insipidus. Case report with autopsy, Endocrinology, 1940, XXVII, 430.
406. FRADISS, L.: Le diabète insipide, Ollier-Henry, Éditeur, Thèse Paris, 1926. BIGGART, J. H.: Anatomical basis for resistance to pituitrin in diabetes insipidus, Jour. Path. and Bact., 1937, XLIV, 305.
407. LEARY, T.: Excess cholesterol as a pathogenic agent, p. 32, Proceed 50th Anniversary, Tufts College Medical School, Tufts Medical Alumni Association, Boston, 1944. The genesis of atherosclerosis, Arch. Path., 1941, XXXII, 507.
408. BROWN, W. E., Jr., and RYNEARSON, E. H.: A procedure for the diagnosis of diabetes insipidus, Proceed Staff Meeting, Mayo Clinic, 1944, XIX, 67.
409. ABEL, J. J., ROUILLIER, C. A. and GEILING, E. M. K.: Further investigations on the oxytocic-pressor-diuretic principle of the infundibular portion of the pituitary gland, Jour. Pharmacol. and Exper. Therap., 1923, XXII, 289.
410. KAMM, O., ALDRICH, T. B., GROTE, I. W., ROWE, L. W. and BUGBEE, E. P.: The active principles of the posterior lobe of the pituitary gland. 1. The demonstration of the presence of the active principles. II. The separation of the two principles and their concentration in the form of potent solid preparations, Jour. Am. Chem. Soc., 1928, L, 573.
411. STEHLE, R. L.: New method for separating pressor and oxytocic substances from posterior lobe of pituitary gland, Jour. Biol. Chem., 1933, CII, 573.
412. PHARMACOPOEIA of the U. S. A. (the U.S.P.) U. S. P. XIII Edition, April, 1947, p. 414.
413. SMITH, F. M.: Diabetes insipidus, treatment by intranasal insufflation of posterior pituitary powder, Jour. Am. Med. Assoc., 1934, CII, 660.
414. CHOAY, A. and CHOAY, L.: Vingt ans de traitement du diabète insipide par prisés nasales de poudre de lobe postérieur d'hypophyse, Presse méd., Paris, 1946, LIV, 500.
415. REES, M. H. and OLMSTED, W. H.: The use of pituitary extracts by mouth in the treatment of diabetes insipidus, Endocrinology, 1922, VI, 230.
416. GEILING, E. M. K. and OLDHAM, F. K.: The neurohypophysis, Jour. Am. Med. Assoc., 1941, CXVI, 302.
417. MOFFAT, W. M.: The effect of pituitrin injections on blood pressure in man, Am. Jour. Med. Sci., 1933, CLXXXVI, 854.
418. STEHLE, R. L.: See reference 411. MELVILLE, K. I.: Electrocardiographic and blood pressure changes induced by posterior

443. McPHEDRAN, H.: Three cases of diabetes insipidus, one associated with toxic goiter, Canad. Med. Assoc. Jour., 1938, XXXIX, 370. The thyroidectomy was partial, personal communication to the author.

444. FERRO-LUZZI, G.: La tiroidectomia nel diabete insipido, *Minerva Med.*, 1937, II, 557.

445. FINDLEY, T., Jr.: Thyroid-pituitary relationship in diabetes insipidus, Ann. Int. Med., 1937, XI, 701.

446. ASTWOOD, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil, Jour. Am. Med. Assoc., 1943, CXXII, 78. ASTWOOD, E. B. and VANDERLAAN, W. P.: Propylthiouracil, Jour. Clin. *Endocrinol.*, 1945, V, 424.

447. REVENO, W. S.: Effect of thiouracil on human tissues, Jour. Clin. Endocrinol., 1945, V, 403.

448. MEYER-NOBLE, K.: Beeinflussung eines Falles von Diabetes insipidus durch Corpus-luteum Extrakt, Münch. med. Wochnschr., 1930, LXXVII, 1844.

449. TEEL, H. M.: *Diuresis in dogs from neutralized alkaline extracts of* the anterior hypophysis, Jour. Am. Med. Assoc., 1929, XCIII, 760. TEEL, H. M. and CUSHING, H.: Studies in the physiological properties of the growth-promoting extracts of the anterior hypophysis, Endocrinology, 1930, XIV, 157.

450. BIASOTTI, A.: Thyroide et action diurétique de l'extrait anté-hypophysaire, Compt. rend. Soc. de Biol., 1934, CXV, 329.

451. TROISIER, J.: Action antipolyurique des hautes doses de folliculine dans le diabète insipide de l'homme, Bull. et Mém. Soc. méd. d. Hôp. de Paris, 1932, XLVIII, 1451.

452. BELTRAMETTI, L.: Die sexualfunktionen in ihren Beziehungen zum *Wasserhaushalt insbesondere zum Diabetes insipidus, Endokrinologie,* 1935, XVI, 241.

453. ASTWOOD, E. B.: Personal communication.

453a. SHAPIRO, B. G.: Control of urinary secretion by the anterior pituitary, Lancet, 1938, II, 1457.

454. BLOTNER, H.: *Effect of* amniotin and antuitrin in diabetes insipidus, New England Jour. Med., 1937, CCXVII, 592.

455. BARNES, B. O., REGAN, J. F. and NELSON, W. O.: Improvement in experimental diabetes following the administration of amniotin, Jour. Am. Med. Assoc., 1933, CI, 926.

456. COLLENS, W. S., SLO-BODKIN, S. G., ROSENBLIETT, S. and BOAS, L. C.: The effect of estrogenic substance on human diabetes, Jour. Am. Med. Assoc., 1936, CVI, 678.

457. SILVESTRI, T.: Diabete insipido e pubertà, Riforma med., 1921, XXXVII, 412.

428a. WEINSTEIN, E. A. and SPINGARN, C. L.: Diabetes insipidus, Jour. Mt. Sinai Hospital, 1940, VII, 90.
429. ROWLAND, R. S.: Xanthomatosis and the reticulo-endothelial system: correlation of unidentified group of cases described as defects in membranous bones, exophthalamos and diabetes insipidus (Christian's syndrome), Arch. Int. Med., 1928, XLII, 611.
430. SCHÜLLER, A. and CHIARI, H.: Ein Fall von Xanthomatose, Wien. klin. Wochnschr., 1930, XLIII, 153.
431. HOFER, K.: Beitrag zur Xanthomatose der Dura Mater und der Schadelknochen, Klin. Wochnschr., 1930, IX, 1302.
432. LEVINSON, A.: Diabetes insipidus, Am. Jour. Dis. Child., 1926, XXXII, 154. MEIJERS, E. J.: Diabetes insipidus in children, Nederl. tijdschr. v. geneesk., 1929, II, 5336. ROWNTREE, L. G.: Diabetes insipidus, Jour. Am. Med. Assoc., 1924, LXXXIII, 399.
433. EBSTEIN, W.: Beiträge zur Lehre von Diabetes insipidus, Deutsch. Arch. f. klin. Med., 1909, XCV, 1.
434. BENARIO, J.: Zur Pathologie und Therapie des Diabetes insipidus, Münch. med. Wochnschr., 1913, LX, 1768.
435. UMBER: Berlin, gesellschaft für Chirurgie, Deutsch. med. Wochnschr., 1922, XLVIII, 1221.
436. CHRISTIE, C. D. and STEWART, G. N.: Study of some cases of diabetes insipidus with special reference to the detection of changes in the blood when water is taken or withheld, Arch. Int. Med., 1922, XXIX, 555.
437. HERRICK, J. B.: Report of a case of diabetes insipidus with marked reduction in the amount of urine following lumbar puncture, Arch. Int. Med., 1912, X, 1.
438. CAMMIDGE, P. J.: Complete recovery from diabetes insipidus, Practitioner, 1920, CV, 244.
439. ALLEN, F. M. and SHERRILL, J. W.: Diet treatment of diabetes insipidus, Jour. Metab. Research, 1923, III, 479.
440. HIRSCH, O. and DEMEL, R.: Ueber Implantation von tierscher und menschlicher Hypophyse bei Diabetes insipidus, Wien. klin. Wochnschr., 1936, XLIX, 523.
441. HIRSCH, O.: Rolle der Hypophyse und des Hypothalamus beim Diabetes insipidus (Beobachtungen am Patienten und Implantationen von Tierischen und menschlichen Hypophysen), Wien. klin. Wochnschr., 1937, L, 229.
441a. AZÉRAD, E.: Sur le traitement du diabète insipide par des implantations de fragments de lobe postérieur d'hypophyse fraîche, Bull. et Mém. Soc. méd. Hôp. de Paris, 1946, LXII, 279.
442. McCONNELL, A. A.: A case of diabetes insipidus influenced by partial thyroidectomy, Irish Jour. Med. Sci., 1936 (Dec.), p. 742.

458. HARVEY, A.: A case of diabetes insipidus permanently cured by an intercurrent attack of measles, Birmingham Med. Rev., 1892, XXXI, 166.
459. ELLIS, C. H. and WIERSMA, C. A. G.: Influence of electronarcosis on secretory activity of the pituitary gland, Proc. Soc. Exper. Biol. and Med., 1945, LVIII, 160.
460. DROUET, P. L., VERAIN, M., GRANDPIERRE, G. and PIERQUIN: Un cas de diabète insipide avec glycosurie; traitement par les ondes courtes sur la région hypophysotubérienne, Bull. et Mém. Soc. méd. d. Hôp. de Paris, 1936, LII, 115.
461. JUDSON, W. E., EPSTEIN, F. H., TINSLEY, C. M., BURROWS, B. A. and WILKINS, R. W.: The hemodynamic and renal functional effects of venous congestion of the limbs in patients with diabetes insipidus, Jour. Clin. Invest., in press.
462. WILKINS, R. W., CULBERTSON, J. W., BURROWS, B. A., TINSLEY, C. M., JUDSON, W. E. and BURNETT, C. H.: Antidiuresis and renal vasoconstriction following venous congestion of the limbs in normal, hypertensive and splanchnicectomized subjects, Jour. Clin. Invest., 1949, XXVIII, 819.
463. BARTSOKAS, S.: À Propos d'une cas de virilisme surrénal avec tumor de la corticale surrénale et diabète insipide chez une fillette de 28 mois, Arch. franç. Pediat., 1947, IV, 266.
464. RALLI, E. P., ROBSON, J. S., CLARKE, D. and HOAGLAND, C. L.: Factors influencing ascites in patients with cirrhosis of the liver, Jour. Clin. Invest., 1945, XXIV, 316.
465. EVERSOLE, W. J., BIRNIE, J. H. and GAUNT, R.: Inactivation of posterior pituitary antidiuretic hormone by the liver, Endocrinology, 1949, L, 378.
466. PORTER, R. J. and MILLER, R. A.: Diabetes insipidus following closed head injury, Jour. Neurol., Neurosurg. and Psychiatry, 1948, XI, 258.
467. MUSSIO-FOURNIER, J. C. and SARALEGUI, J. P.: Laurence-Moon-Biedl Syndrome avec Diabète insipide, maladie de Legg-Perthes et Doight de Telford Smith, Bull. et Mem. Soc. Méd. d. Hôp. de Paris, 1948, LXIV, 34.
468. DANCIS, J., BIRMINGHAM, J. R. and LESLIE, S. H.: Congenital diabetes insipidus resistant to treatment with pitressin, Am. Jour. Dis. Child., 1948, LXXV, 316.
469. FALTA, W. and TITZE, H.: Behandlung des Diabetes insipidus mit Weckmitteln, Wien. klin. Wochnschr., 1949, LXI, 164.
470. WINTER, J. A.: Diabetes insipidus, amelioration after tonsillectomy, Am. Jour. Pediat., 1948, XXXII, 78.